

1271779

UNITED STATES PATENT AND TRADEMARK OFFICE

TO AND TWO WILSON THERESA PRESENTS: SMALL, COMMERCE

UNITED STATES DEPARTMENT OF COMMERCE

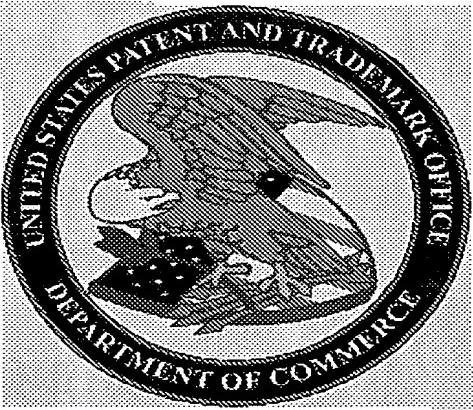
United States Patent and Trademark Office

January 10, 2005

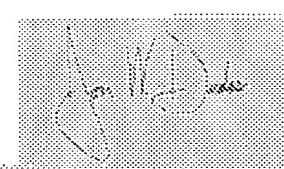
THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE.

BEST AVAILABLE COPY

APPLICATION NUMBER: 60/528,846
FILING DATE: *December 11, 2003*
RELATED PCT APPLICATION NUMBER: PCT/US04/41580



Certified By



Jon W Dudas

Under Secretary
of Commerce for Intellectual Property
and Acting Director of the
United States Patent and Trademark Office

16085
121103
U.S.PTO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAIL STOP PROVISIONAL APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

17510 U.S.PTO
60/528846

121103

PROVISIONAL APPLICATION COVER SHEET

Sir:

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53(c).

Docket Number

CL001492-P

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Name	RESIDENCE (City and either State or Foreign Country)
ELROD	Kyle	C.	San Mateo, CA - U.S.A.

TITLE OF THE INVENTION

COMBINATION THERAPY UTILIZING CATHEPSIN S INHIBITORS

CORRESPONDENCE ADDRESS

Customer Number or Bar Code Label

23519

(Insert Customer No. or Attach bar code label here)

or Correspondence address below

ENCLOSED APPLICATION PARTS (check all that apply)

118 Pages Specification Other (specify)47 Pages Claims

-1 Sheet Title Page w/Certificate of Mailing

1 Page Abstract

-Return Postcard

n/a Printed Sheets of Drawingsn/a Pages Sequence Listing

METHOD OF PAYMENT (check one)

 A check is enclosed to cover the Provisional Filing FeePROVISIONAL
FILING FEE
AMOUNT (\$)

\$160.00

 The Commissioner is hereby authorized to chargefiling fees and credit Deposit Account Number: 50-0970

Was the invention made by an agency of the United States Government or under a contract with an agency of the

United States Government?

 No. Yes, the name of the U.S. Government agency and the Government contract number are: _____

The above FEE is believed to be correct. However, the Commissioner is authorized to charge any deficiencies or credit any overpayments to Deposit Account No. 50-0970.

Respectfully submitted,


Rekha Bansal, Reg. No.: 36,440

Date: December 11, 2003

Express Mail label No. EV151048495US
Date of Deposit: December 11, 2003

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicate below and is addressed to Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Debra K. Bowen Date: 12/11/03
Debra K. Bowen

COMBINATION THERAPY UTILIZING CATHEPSIN S INHIBITORS

Inventor

Kyke C. Elrod

COMBINATION THERAPY UTILIZING CATHEPSIN S INHIBITORS

Field of Invention

The present invention is directed to the use of Cathepsin S inhibitors in combination with a
5 biologic that elicits an immune response in patients receiving the biologic.

State of the Art

In the past decade there has been an increase in the use of biologics in the treatment of diseases. For example, Embrel® is used in the treatment of rheumatoid arthritis, ankylosing
10 spondylitis, and juvenile rheumatoid arthritis. Referon®-A is used in the treatment of diseases such as chronic hepatitis C, hairy cell leukemia, and AIDS -related sarcoma.

Although biologics can be less toxic than small molecule therapeutics they suffer from several drawbacks. The first drawback is that many of the biological agents induce the production of specific immunoglobulins. These immunoglobulins bind with one or more epitopes on the
15 biological agents thereby rendering the biological agents less effective in many cases. For example, 10% of patients taking Remicade® generate neutralizing antibodies, 45% of patients taking Betaseron® were found to have serum-neutralizing activity, and 25% of patients taking Referon® -A generated neutralizing antibodies. It was recently reported that neutralizing antibodies against interferon Beta used for treating multiple sclerosis reduces the clinical effect of
20 the drug (see Lancet, dated October 11, 2003). In fact, host immune response prevents effective application of retroviral therapy (see *Journal of Virology* 72, 2388–2397, *European Journal of Immunology* 27, 653–659). A side effect of antibody binding is the activation of humoral or cell-mediated defenses (e.g., complement, mast cells, and macrophages). Therefore, a second consequence of antibody production is the generation of a host reaction that can be deleterious to
25 patient. Such reactions include inflammation at the site of injection, the binding of neutralizing antibodies to the host's own proteins or in the case of repeated exposure a lethal systemic anaphylaxis. As an example, a number of patients taking Epogen® exhibit pure red cell aplasia as consequence of antibodies.

Currently, this problem is being handled either by administering methotrexate along with
30 the biologic, stopping the use of the biologic, increasing the dose of the biologic to induce tolerance or reengineering the biologic agent to reduce immunogeneity. All these approaches

- 3 are undesirable; methotrexate is associated with severe side effects such as liver damage, nerve
damage, kidney damage, and hair loss, utilizing higher doses of the biologic results in higher
medical costs and reengineering can increase drug development time again incurring increased
medical expense. Accordingly, there is a need for therapeutic agents that can be co-administered
5 with the biologics to prevent or ameliorate the generation of immune response by the biologics
without adverse side effects.

The present invention fulfills this and related needs.

DETAILED DESCRIPTION

10 This invention is directed to a method of treating a patient undergoing treatment with a
biologic wherein the biologic causes a deleterious immune response in the patient comprising
administering to the patient a Cathepsin S inhibitor. Preferably, the immune response is mediated
by MHC class II molecules. The Cathepsin S inhibitor can be administered prior to,
simultaneously, or after the administration of the biologic.

15 Preferably, the biologic is a protein or an antibody, preferably a monoclonal antibody.
More preferably, the biologic is Remicade®, Refacto®, Referon-A®, Factor VIII, Factor VII,
Betaseron®, Epopen®, Embrel®, Interferon beta, Botox®, Fabrazyme®, Elspar®, Cerezyme®,
Myobloc®, Aldurazyme®, Verluma®, Interferon alpha, Humira®, Aranesp®, Zevalin® or OKT3.

20 In a second aspect, this invention is directed to a method of treating immune response in an
animal that is caused by administration of a biologic to the animal which method comprises
administering to the animal in need of such treatment a therapeutically effective amount of a
Cathepsin S inhibitor.

25 In a third aspect, this invention is directed to a method of conducting a clinical trial for a
biologic comprising administering to an individual participating in the clinical trial a Cathepsin S
inhibitor with the biologic.

In a fourth aspect, this invention is directed to a method of prophylactically treating a
person undergoing treatment with a biologic with a Cathepsin S to treat the immunological effects
caused by the biologic.

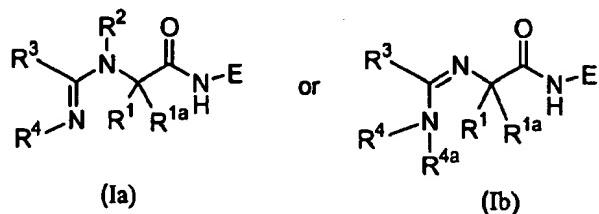
30 In a fifth aspect, this invention is directed to a method of determining the loss in the efficacy
of a biologic in an animal due to the immune response caused by the biologic comprising
administering the biologic to the animal in the presence and absence of a Cathepsin S inhibitor.

In a sixth aspect, this invention is directed to a method of improving efficacy of a biologic in an animal comprising administering the biologic to the animal with a Cathepsin S inhibitor.

In an seventh aspect, this invention is directed to the use of a Cathepsin S inhibitor for the manufacture of a medicament for combination therapy with a biologic, wherein the Cathepsin S inhibitor treats the immune response caused by the biologic.

Preferably, the Cathepsin S inhibitor is:

(a) a compound of Formula (Ia) or (Ib):



10 wherein:

E is:

15 (i) $-C(R^5)(R^6)X^1$ where X^1 is $-CHO$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$,
 $-C(R^7)(R^8)R^{10}$, $-C(O)C(O)R^{10}$, $-CH=CHS(O)_2R^{10}$, $-C(R^7)(R^8)C(R^7)(R^8)OR^{10}$, $-C(R^7)(R^8)CH_2OR^{10}$,
 $-C(R^7)(R^8)C(R^7)(R^8)R^{10}$, $-C(R^7)(R^8)CH_2N(R^{11})SO_2R^{10}$, $-C(R^7)(R^8)CF_2C(O)NR^{10}R^{11}$,
 $-C(R^7)(R^8)C(O)NR^{10}R^{11}$, $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2OR^{11}$,
 $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2NR^{10}R^{11}$, or .

(ii) $-C(R^{5a})(R^{6a})CN;$

where:

R^5 and R^{5a} are independently hydrogen or alkyl; and

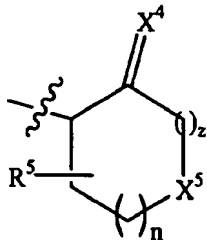
20 R⁶ and R^{6a} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -alkylene-X-R¹² (where X is -O-, -NR¹³-, -S(O)_{n1}-, -CONR¹³-, -NR¹³CO-, -NR¹³C(O)O-, -NR¹³CONR¹³-, -OCONR¹³-, -NR¹³SO₂-, -SO₂NR¹³-, -NR¹³SO₂NR¹³-, -CO-, -OCO-, or -C(O)O- where n1 is 0-2, R¹² hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl) and each R¹³ is hydrogen or alkyl wherein the aromatic or alicyclic ring in R⁶ and R^{6a} is optionally substituted with one, two, or three R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino.

25

- nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in R^a is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alcoxycarbonyl; or
- 5 R⁵ and R⁶ and R^{5a} and R^{6a} taken together with the carbon atom to which both R⁵ and R⁶ and R^{5a} and R^{6a} are attached form (i) cycloalkylene optionally substituted with one or two R^b independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alcoxycarbonyl, or aryloxycarbonyl, or (ii) heterocycloalkylene optionally substituted with one to four alkyl or one or two R^c independently selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)_{n2}R¹⁴, -alkylene-S(O)_{n2}-R¹⁵, -COOR¹⁶, -alkylene-COOR¹⁷, -CONHR¹⁸R¹⁹, or -alkylene-CONHR²⁰R²¹ (where n2 is 0-2 and R¹⁴-R¹⁷, R¹⁸ and R²⁰ are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and R¹⁹ and R²¹ are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alcoxycarbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;
- 10 R⁷ is hydrogen or alkyl;
- 15 R⁸ is hydroxy; or
- 20 R⁷ and R⁸ together form oxo;
- 25 R⁹ is hydrogen, halo, alkyl, aralkyl or heteroaralkyl; and
- 30 R¹⁰ is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in R¹⁰ is optionally substituted with one, two, or three R^d independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alcoxycarbonyl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, aralkyl, heteroaryl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl wherein the aromatic or alicyclic ring in R^d is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alcoxycarbonyl, amino, alkylamino, or dialkylamino; and

R¹¹ is hydrogen or alkyl; or

(iii) a group of formula (a):



5

(a)

where:

n is 0, 1, or 2;

z is 1;

X⁴ is selected from -NR²²-, -S-, or -O- where R²² is hydrogen, alkyl, or alkoxy; and

10 X⁵ is -O-, -S-, -SO₂-, or -NR²³- where R²³ is selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, -S(O)₂R²⁴, -alkylene-S(O)_{n3}-R²⁵, -COOR²⁶, -alkylene-COOR²⁷, -CONR²⁸R²⁹, or -alkylene-CONR³⁰R³¹ (where n3 is 0-2 and R²⁴-R²⁷, R²⁸ and R³⁰ are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 15 cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and R²⁹ and R³¹ are independently hydrogen or alkyl) where the aromatic or alicyclic ring in X⁵ is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl;

20 R⁵ is as defined above;

R¹ is hydrogen or alkyl;

R^{1a} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkylalkyl, or -alkylene-X²-R³² [wherein X² is -NR³³-, -O-, -S(O)_{n4}-, -CO-, -COO-, -OCO-, -NR³³CO-, -CONR³³-, -NR³³SO₂-, -SO₂NR³³-, -NR³³COO-, -OCONR³³-, -NR³³CONR³⁴, or -NR³³SO₂NR³⁴- (where R³³ and R³⁴ are independently hydrogen, alkyl, or acyl and n4 is 0-2) and R³² is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, 25 aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl] wherein said alkylene chain is optionally substituted with one to six halo and wherein the aromatic or alicyclic

- 3 ring in R^{1a} is optionally substituted with one, two, or three R^e independently selected from alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminocarbonyl, aminosulfonyl, acyl, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, monosubstituted amino,
- 5 disubstituted amino, or acyl; or

R¹ and R^{1a} together with the carbon atoms to which they are attached form cycloalkylene or heterocycloalkylene ring wherein said cycloalkylene or heterocycloalkylene is optionally substituted with one or two R^f independently selected from alkyl, halo, haloalkyl, hydroxyalkyl, keto, or -SO₂R where R is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl where the aromatic or alicyclic ring in R^f is optionally substituted with one, two, or three substitutents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, halo, carboxy, or alkoxycarbonyl;

R² is hydrogen or alkyl;

R³ is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,

15 heterocycloalkyl, heterocycloalkylalkyl, amino, mono or disubstituted amino, or -alkylene-X³-R³⁵ [wherein X³ is -NR³⁶-, -O-, -S(O)_{n5}-, -CO-, -COO-, -OCO-, -NR³⁶CO-, -CONR³⁶-, -NR³⁶SO₂-, -SO₂NR³⁶-, -NR³⁶COO-, -OCONR³⁶-, -NR³⁶CONR³⁷-, or -NR³⁶SO₂NR³⁷- (where R³⁶ and R³⁷ are independently hydrogen, alkyl, or acyl and n5 is 0-2) and R³⁵ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the aromatic or 20 alicyclic rings in R³ are optionally substituted by one, two, or three R^g independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, 25 arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R^g are optionally substituted with one, two, or three R^h wherein R^h is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, 30 alkylamino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;

R⁴ is hydrogen, alkyl, hydroxy, nitrile, or -(alkylene)n₆-X⁶-R³⁸ (where X⁶ is -O-, -NR³⁹-, -S(O)_{n7}-, -NR³⁹CO-, -CO-, or -OC(O)- where n6 is 0 or 1, n7 is 0-2, and R³⁹ is hydrogen or alkyl

- and R³⁸ is hydrogen, alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranlyl, thiopyranlyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl,
- 5 benzoxazolyl, or quinoxaliny where R³⁸ is optionally substituted with one, two, or three Rⁱ independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, monosubstituted amino, disubstituted amino, carboxy, alkoxy carbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, or heterocycloalkyl where the aromatic or alicyclic ring in Rⁱ is optionally substituted with one or
- 10 two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl; or

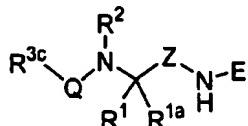
R³ and R⁴ in (Ia) or (Ib) together with the atoms to which they are attached form heteroaryl or heterocycloalkyl ring optionally fused to an aryl or heteroaryl ring wherein said rings are optionally substituted on the aromatic and/or non-aromatic portion of the rings with one, two, or
15 three R^j;

each R^j and R^{4a} is independently:

- hydrogen, alkyl optionally interrupted by one or two N, O, C(O), S, S(O), or S(O)₂ and optionally substituted by amino, hydroxy, halo, alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranlyl, thiopyranlyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxaliny;

halo, alkoxy, alkylthio, hydroxy, carboxy, aryl, aryloxy, aroyl, heteroaryl, alkanoyl, - C(O)OR where (R is hydrogen, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl,
25 heteroaryl, heteroarylalkyl, aryl, arylalkyl, aminoalkyl, heterocycloalkyl, or heterocycloalkylalkyl), aminocarbonyl, aminosulfonyl, alkylsulfonyl, aryloxycarbonyl, benzyloxycarbonyl, alkanoylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxy carbonylamino, aroylamino, amino, alkylamino, dialkylamino, alkylthio, arylthio, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, cycloalkyl, 30 benzyloxy, or ureido wherein each of the aforementioned groups in R^{4a} and R^j is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, alkyl, alkoxy, haloalkyl, haloalkoxy, oxo, carboxy, nitrile, nitro or NH₂C(O)-; or

5 (b) a compound of Formula (II):



(II)

where:

E, R¹, and R^{1a} are as defined above;

5 Z is -CO- or -CH₂SO₂-; or

Q is -CO-, -SO₂-, -OCO-, -NRCO-, or -NRSO₂- where R is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

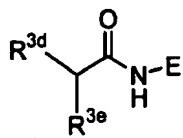
10 R^{3c} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X⁸-R⁴⁰ [wherein X⁸ is -NR⁴¹-, -O-, -S(O)_{n8}-, -CO-, -COO-, -OCO-, -NR⁴¹CO-, -CONR⁴¹-, -NR⁴¹SO₂-, -SO₂NR⁴¹-, -NR⁴¹COO-, -OCONR⁴¹-, -NR⁴¹CONR⁴²-, or -NR⁴¹SO₂NR⁴²- (where R⁴¹ and R⁴² are independently hydrogen, alkyl, or acyl and n8 is 0-2) and R⁴⁰ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the alkylene chain in R^{3c} is optionally substituted with one to three halo atoms and the aromatic and alicyclic rings in R^{3c} are optionally substituted by one, two, or three R^k independently selected from alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino,

15 aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, aralkylaminosulfonyl, aminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R^k are optionally substituted with one, two, or three R¹ wherein R¹ is independently selected from

20 alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;

25

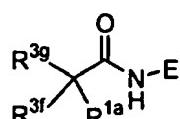
(c) a compound of Formula (III):



(III)

where E is as defined above;

- R^{3d} and R^{3e} are independently -alkylene-X⁹-R⁴³ [wherein X⁹ is bond, -NR⁴⁴-, -O-, -S(O)_{n9}-
 5 , -CO-, -COO-, -OCO-, -NR⁴⁴CO-, -CONR⁴⁴-, -NR⁴⁴SO₂-, -SO₂NR⁴⁴-, -NR⁴⁴COO-, -OCONR⁴⁴-,
 -NR⁴⁴CONR⁴⁵-, or -NR⁴⁴SO₂NR⁴⁵- (where R⁴⁴ and R⁴⁵ are independently hydrogen, alkyl, or acyl
 and n9 is 0-2) and R⁴³ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
 heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl] wherein the alkylene chain is
 optionally substituted with one to three halo atoms and the aromatic or alicyclic rings in R^{3d} and
 R^{3e} are optionally substituted by one, two, or three R^m independently selected from alkyl, halo,
 10 hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, carboxy,
 alcoxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alcoxycarbonylamino,
 alkylcarbamoyloxy, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl,
 dialkylaminosulfonyl, aminocarbonyl, amino, monosubstituted or disubstituted amino and one
 substituent selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,
 15 heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio,
 arylsulfonyl, arylsulfinyl, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino,
 arylaminosulfonyl, or aralkylaminosulfonyl, wherein the aromatic or alicyclic ring in R^m is
 optionally substituted with one, two, or three Rⁿ wherein Rⁿ is independently selected from alkyl,
 halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl,
 20 aminoalkyl, alkylthio, alkylsulfonyl, alkylsulfonylamino, arylsulfonylamino,
 heteroarylsulfonylamino, heteroaralkylsulfonylamino, amino, monosubstituted amino,
 dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alcoxycarbonyl;
 (d) a compound of Formula (IV):



(IV)

25 where:

E, and R^{1a} are as defined above;

- R^{3f} is hydrogen;
- R^{3g} is hydrogen, fluoro, -OR⁴⁶ or -NR⁴⁷R⁴⁸ where:
 - R⁴⁶ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -(alkylene)n₁₀-X¹⁰-R⁴⁹ [wherein n₁₀ is 0 or 1, X¹⁰ is -CO- or -CONR⁵⁰- where R⁵⁰ is hydrogen, alkyl, or alkoxyalkyl, and R⁴⁹ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl or R⁴⁹ and R⁵⁰ together with the nitrogen atom to which they are attached from heterocycloalkyl], or -alkylene-X¹¹-R⁵¹ [wherein X¹¹ is -NR⁵²-, -O-, -S(O)_{n11}-, -COO-, -OCO-, -NR⁵²CO-, -NR⁵²SO₂-, -SO₂NR⁵²-, -NR⁵²COO-, -OCONR⁵²-, -NR⁵²CONR⁵³-, or -NR⁵²SO₂NR⁵³- [where n₁₁ is hydrogen or alkyl, R⁵² is hydrogen or alkyl, and R⁵¹ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl or R⁵¹ and R⁵² or R⁵³ together with the nitrogen atom to which they are attached from heterocycloalkyl] wherein the alkylene chain is optionally substituted with one to three halo atoms and the aromatic or alicyclic rings in R⁴⁶ are optionally substituted by one, two, or three R° independently selected from alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, carboxy, alkoxy carbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy carbonylamino, alkylcarbamoyloxy, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, aminocarbonyl, amino, monosubstituted or disubstituted amino and one radical selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio, arylsulfonyl, arylsulfinyl, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, or aralkylaminosulfonyl wherein the aromatic and alicyclic rings in R° are optionally substituted with one, two, or three R^p wherein R^p is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxy carbonyl; R⁴⁷ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl; and R⁴⁸ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,

- heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl provided that one of R⁴⁷ and R⁴⁸ is other than hydrogen and wherein the aromatic or alicyclic rings in R⁴⁷ and R⁴⁸ are optionally substituted by one, two, or three R⁹ independently selected from alkyl, halo, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy,
- 5 carboxy, alkoxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkylcarbamoyloxy, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, amino, monosubstituted or disubstituted amino and one radical selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio, arylsulfonyl, arylsulfinyl,
- 10 aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, or aralkylaminosulfonyl wherein the aromatic and alicyclic rings are optionally substituted with one, two, or three R¹ wherein R¹ is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido,
- 15 or alkoxycarbonyl; or
- R^{3f} and R^{3g} are fluoro; or
- (e) 7-(2,2-dimethylpropyl)-6-thiophen-2-ylmethyl-7H-pyrrolo-[2,3-d]pyrimidine-2-carbonitrile;
- or
- a pharmaceutically acceptable salts thereof.
- 20 Compounds generically and specifically disclosed in U.S. Patents 6,353,017B1, 6,525,052 B2, 6,395,897B1, 6,313,117 B1, 6,635,621, 6,617,426, 6,698,057, 6,608,030, 6,593,327, 6,583,155, 6,579,896, 6,576,630, 6,569,847, 6,531,612, 6,525,036, 6,506,733, 6,492,362, 6,476,026, 6,462,076, 6,455,502, 6,420,364, 6,395,897, 6,287,840, 6,117,870, 6,030,947, 6,004,933, 5,976,858, 5,776,718, and 6,635,633 B2, PCT applications publication Nos. WO 00/55144, 00/55126, 00/07145, 00/55125, 01/19796, 01/19816A1, 01/49288, 01/77073, 02/051983, 02/098850, 02/098406, 02/23784, 02/070519, 02/080920, 02/069901, 03/075836, 02/100849A2, 03/024924, 03/037892A1, 03/029,200A2, 03/024923, 03/041649, and 02/0204485 A1, PCT application No. US03/19990 and US applications publication Nos. 2002/0040019 A1, 2003/0069240 A1, 2003/0114437 A1, 2003/0186962, 2003/0119827 A1, and 2003/0087939 A1,
- 25 00/55144, 00/55126, 00/07145, 00/55125, 01/19796, 01/19816A1, 01/49288, 01/77073, 02/051983, 02/098850, 02/098406, 02/23784, 02/070519, 02/080920, 02/069901, 03/075836, 02/100849A2, 03/024924, 03/037892A1, 03/029,200A2, 03/024923, 03/041649, and 02/0204485 A1, PCT application No. US03/19990 and US applications publication Nos. 2002/0040019 A1, 2003/0069240 A1, 2003/0114437 A1, 2003/0186962, 2003/0119827 A1, and 2003/0087939 A1,
- 30 2003/0203900, 2003/0199506, 2003/0186962, 2003/0158406, 2003/0158256, 2003/0158231, 2003/0153508, 2003/0144234, 2003/0119827, 2003/0119788, 2003/0114437, 2003/0105099, 2003/0100550, 2003/0096796, 2003/0092634, 2003/0087939, 2003/0078419, 2003/0073672,

2003/0069240, 2002/0164765, 2002/0147189, 2002/0137932, 2002/0115656, 2002/0091259, 2002/0086996, 2002/0064856, 2002/0058809, 2002/0055497, 2002/0052378, 2002/0040020, 2002/0040019, 2002/0016361, 2001/0041700, and 2001/0008901 can also be used to practice the present invention. The compounds disclosed in the above patents and patent applications are

5 incorporated herein by reference in their entirety.

Preferably, the Cathepsin S inhibitor is selected from:

N-[1*R*-(benzooxazol-2-yl-2-hydroxy-1*S*-phenethylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;

2*S*-acetylamino-*N*-(2-oxazol-2-yl-2-hydroxy-1*S*-phenethyl)-3-

10 cyclohexylpropionamide;

2*S*-acetylamino-*N*-(2-oxazol-2-yl-2-hydroxy-1*S*-phenethyl)-3-cyclohexylpropionamide;

2*S*-acetylamino-*N*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethyl]-3-cyclohexylpropionamide;

2*S*-acetylamino-*N*-(*S*-benzothiazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropion-

15 amide;

N-[1*S*-(1*S*-phenethyl-2-benzooxazol-2-yl-1-oxoethylcarbamoyl)-2-naphth-2-ylethyl]-piperidine-4-carboxamide;

2*S*-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropionamide;

20 *tert*-butyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl carbamate;

2*S*-acetylamino-*N*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropyl]-3-cyclohexylpropionamide;

benzyl 1*S*-(benzooxazol-2-ylcarbonylmethylcarbamoyl)-3-methylbutylcarbamate;

25 benzyl 1*S*-(5-phenylbenzooxazol-2-ylcarbonylmethylcarbamoyl)-3-methylbutylcarbamate;

2*S*-acetylamino-*N*-(1*S*-oxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropionamide;

2-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-phenylpropionamide;

benzyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-naphthalen-2-ylethylcarbamate;

30 2-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-(2-fluorophenyl)-propionamide;

- 2*S*-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-2-methyl-3-phenylpropionamide;
- 5 *tert*-butyl 1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-phenylpropylcarbamate;
- 10 2-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-3*S*-carboxamide;
- 15 2*S*-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-(2-chlorophenyl)-propionamide;
- 20 2-acetylamino-*N*-(1-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-(2-trifluoromethyl-phenyl)propionamide;
- 25 benzyl 1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methylbutylcarbamate;
- 30 *N*-{1*S*-[1*S*-(benzoxazol-2-ylcarbonyl)-3-phenylpropylsulfamoylmethyl]-3-methylbutyl}acetamide;
- 35 benzyl 1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methylbutylcarbamate;
- 40 *N*-[1-(1-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methylbutyl]-acetamide;
- 45 *tert*-butyl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzylsulfanyl)ethylcarbamate;
- 50 *tert*-butyl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfanylethylcarbamate;
- 55 *N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzylsulfanyl)ethyl]isonicotinamide;
- 60 9H-fluoren-9-ylmethyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethylcarbamate;
- 65 *tert*-butyl 4-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzylsulfanyl)ethylcarbamoylpiperidine-1-carboxylate;
- 70 benzyl 4-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 75 *N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]-tetrahydropyran-4-carboxamide;

- 5 *N*-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]-nicotinamide;
- 10 *N*-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]pyrazine-2-carboxamide;
- 15 4-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 20 *N*-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethyl]-isonicotinamide;
- 25 *tert*-butyl 4-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(3-methylpyrid-2-ylmethylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 30 tetrahydropyran-4-yl 1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfanylethylcarbamate;
- 35 *N*-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethyl]tetrahydropyran-4-carboxamide;
- 40 *N*-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethyl]-6-hydroxynicotinamide;
- 45 *tert*-butyl 4-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyano-benzylsulfonyl)ethylcarbamoylpiperidine-1-carboxylate;
- 50 *N*-[1*R*-(2-benzooxazol-2-1-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzyl-sulfonyl)ethyl]isonicotinamide;
- 55 *tert*-butyl 1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzyl-sulfonylethylcarbamate;
- 60 *N*-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-pyridin-3-yl-methylsulfonylethyl]pyrazine-2-carboxamide;
- 65 *N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-cyclohexyl-2*S*-(3-pyridin-3-yl-ureido)propionamide;
- 70 *N*-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethyl]morpholine-4-carboxamide;
- 75 *tert*-butyl 4-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 80 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-benzyl-sulfonylethyl]tetrahydropyran-4-carboxamide;

- 5 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]nicotinamide;
- 10 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]pyrazine-2-carboxamide;
- 15 *tert*-butyl 4-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 20 *tert*-butyl 4-[1*S*-(1-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methyl-pyridin-2-ylmethylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 25 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzyl-sulfonyl)ethyl]isonicotinamide;
- 30 tetrahydropyran-4-yl 1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethylcarbamate;
- 35 benzyl 4-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 40 *N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexyl-2*S*-(3-pyridin-3-yl-ureido)propionamide;
- 45 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-morpholine-4-carboxamide;
- 50 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl-isonicotinamide;
- 55 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-tetrahydropyran-4-carboxamide;
- 60 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-6-hydroxynicotinamide;
- 65 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]morpholine-4-carboxamide;
- 70 *N*-[1*R*-(2-benzoxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-benzylsulfonyl-ethyl]morpholine-4-carboxamide;
- 75 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(3,5-dimethylisoxazol-4-yl-methylsulfonyl)ethyl]morpholine-4-carboxamide;
- 80 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(3,5-dimethylisoxazol-4-yl-methylsulfonylethyl)]isonicotinamide;

- 5 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethyl]piperidine-4-carboxamide;
- 10 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-piperidine-4-carboxamide hydrochloride;
- 15 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]piperidine-4-carboxamide;
- 20 *N*-(1*S*-benzoxazol-2-ylcarbonylbutyl)-2*R*-methylsulfonylamino-3-benzylsulfonylpropionamide;
- 25 Methyl 1*R*-(1*S*-benzoxazol-2-ylcarbonylbutylcarbamoyl)-2-benzylsulfonylethyl-
- 30 Carbamate;
- 35 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylbutylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- 40 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-1*S*-butyl-2-hydroxyethyl)-3-cyclohexylpropionamide;
- 45 2*S*-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonylpentyl)-3-cyclohexylpropionamide;
- 50 *tert*-butyl 1*S*-[1-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]carbamate;
- 55 2*S*-acetylamino-*N*-(1-benzoxazol-2-ylcarbonyl)-3-phenylpropyl)-3-cyclohexylpropionamide;
- 60 2*S*-acetylamino-*N*-(1-benzoxazol-2-ylcarbonylcyclobutyl)-3-cyclohexylpropionamide;
- 65 2*S*-acetylamino-*N*-(1*R*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropionamide;
- 70 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-2-hydroxy-1*R*-phenylpropyl)-3-cyclohexylpropionamide;
- 75 *N*-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-3*H*-imidazole-4-carboxamide;
- 80 *N*-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenylethylethylcarbamoyl)-2-cyclohexylethyl]-3*H*-imidazole-4-carboxamide;
- 85 *tert*-butyl 1*R*-(1-benzoxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfonylethyl-
- 90 carbamate;
- 95 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-o-tolylmethylsulfonylethyl]morpholine-4-carboxamide;

- N-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-chlorobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 5 N-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-o-tolylmethylsulfonylethyl]morpholine-4-carboxamide;
- 10 N-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-chlorobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(2-benzoxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-o-tolylmethylsulfonylethyl]morpholine-4-carboxamide;
- 15 N-[1*R*-(2-benzoxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-(2-chlorobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(2-benzoxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 20 N-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]piperidine-4-carboxamide;
- N-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*R*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- 25 N-[1*R*-(1-benzoxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;
- benzyl 1*S*-(2-benzoxazol-2-yl-2-hydroxyethylcarbamoyl)-3-methylbutylcarbamate;
- 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-1*S*-methyl-2-oxoethyl)-3-cyclohexylpropionamide;
- 30 *tert*-butyl 1*R*-(1-benzoxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfanylethylcarbamate;

- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- N-[1-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-3-phenylsulfonylpropyl]-morpholine-4-carboxamide;
- 5 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]morpholine-4-carboxamide;
- 10 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]morpholine-4-carboxamide;
- 2-[2-(1-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-morpholin-4-ylcarbonylamino)-ethanesulfonylmethyl]pyridine-1-oxide;
- N-[3-phenylsulfonyl-1-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)propyl]-morpholine-4-carboxamide;
- 15 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]isonicotinamide;
- 20 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl)-ethyl]morpholine-4-carboxamide;
- 2-[2*R*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2-morpholin-4-ylcarbonylamino-ethysulfonylmethyl]pyridine-1-oxide;
- 1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylcarbamate;
- 25 2*R*-[3,3-bis(2-methoxyethyl)ureido]-N-(1*S*-benzooxazol-2-ylcarbonylpentyl)-3-benzylsulfonylpropionamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]isonicotinamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;
- 30 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]isonicotinamide;

- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;
- N-[1*R*-(1-benzooxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;
- 5 N-[1*R*-(1-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-3-ylmethylsulfonylethyl]pyrazine-2-carboxamide;
- N-[1-(1-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]piperidine-4-carboxamide;
- 10 N-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]azetidine-3-carboxamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl)butylcarbamoyl)-2-pyridin-3-ylmethylsulfonylethyl]morpholine-4-carboxamide;
- N-1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethyl]-piperazine-1-carboxamide;
- 15 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylesulfonylpropylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 20 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-benzylsulfonylethyl]piperazine-1-carboxamide;
- N-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropyl)-2*R*-methylsulfonylamino-3-benzylsulfonylpropionamide;
- methyl 1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-2-ylmethyl-sulfonylethylcarbamate;
- 25 methyl 1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-benzylsulfonylethylcarbamate;
- N-(1*S*-benzooxazol-2-ylcarbonylpentyl)-2*R*-[3,3-di(2-methoxyethyl)ureido]-3-pyridin-2-yl-methylsulfonylpropionamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylbutilcarbamoyl)-2-(2-methoxybenzylsulfonyl)-ethyl]morpholine-4-carboxamide;
- 30 N-(1*S*-benzooxazol-2-ylcarbonylbutilcarbamoyl)-2*R*-(3,3-dimethylureido)-3-(2-methoxybenzylsulfonyl)propionamide;

- N-(1*S*-benzoxazol-2-ylcarbonylbutyl)-2-methylsulfonylamino-3-(2-methoxybenzylsulfonyl)propionamide;
- benzyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutylcarbamate;
- 5 N-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutyl]acetamide;
- benzyl 1*S*(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutylcarbamate;
- 10 N-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutyl]acetamide;
- 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-cyclohexylpropionamide;
- tert-butyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl]-2-cyclohexylethyl)-carbamate;
- 15 2-acetylamino-*N*-2-benzoxazol-2-yl-1,1-dimethyl-2-oxoethyl)-3-cyclohexylpropionamide;
- benzyl 1*S*-[2-(5-phenylbenzoxazol-2-yl)-2-hydroxyethylcarbamoyl]-3-methylbutylcarbamate;
- 1*N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenyethylethyl)-2-bicyclo[2.2.1]hept-2-ylacetamide;
- 20 acetamide;
- N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-2-naphthalen-1-ylacetamide;
- N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-phenylpropionamide;
- methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]-4,5-dihydrooxazole-4*S*-carboxylate;
- 25 methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]oxazole-4-carboxylate;
- N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethyl)-4-cyclohexylbutyramide;
- methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]-4,5-dihydrooxazole-4*R*-carboxylate;
- 30 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-(2-trifluoromethylphenyl)propionamide;

- methyl 1-(1-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethylcarbamate;
- 5 *N*-(1-benzoazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexyl-2-methylsulfonylaminopropionamide;
- benzyl 1-(1-benzoazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-2-methylbutylcarbamate;
- 10 *N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]thiophene-3-carboxamide;
- 15 *N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-(2-methylpyrid-3-ylmethylsulfonyl)ethyl]nicotinamide;
- 20 *N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethyl]azetidine-3-carboxamide;
- tert-butyl 1*R*-(1-benzoazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylcarbamate;
- 25 tert-butyl 1*R*-(1*S*-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(4-trifluoromethylpyrid-3-ylmethylsulfonyl)ethylcarbamate;
- 30 *N*-[1*R*-(1-benzoazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylmorpholine-4-carboxamide;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-3-ylmethylsulfonyl-ethyl]isonicotinamide;
- methyl 1*R*-(1*S*-benzoazol-2-ylcarbonylbutylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethylcarbamate;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;
- N*-(1*R*-benzoazol-2-ylcarbonylpropyl)-2-(3,3-dimethylureido)-3-(2-methoxybenzylsulfonyl)propionamide;
- methyl 1*R*-(1*S*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethylcarbamate;
- N*-(1-benzoazol-2-ylcarbonylpentyl)-2*R*-[3,3-bis(2-methoxyethyl)ureido]-3-pyridin-3-ylmethylsulfonylpropionamide;
- N*-(1*S*-benzoazol-2-ylcarbonylpentyl)-2*R*-[3,3-bis(2-methoxyethyl)ureido]-3-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)propionamide;

- N-(1*S*-benzoxazol-2-ylcarbonylpropyl)-3-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)-2*R*-methylsulfonylaminopropionamide;
- 5 methyl 1*R*-(1*S*-benzoxazol-2-ylcarbonylpropylcarbamoyl)-2-(3,5-dimethylisoxazol-4-yl-methylsulfonyl)ethylcarbamate;
- N*-[1*R*-(1-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl-ethyl]isonicotinamide;
- 4-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl-ethylcarbamoyl]pyridine-1-oxide;
- 10 benzyl 1*S*-[2-(4,5-dihydrooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1*S*-[2-(1*H*-benzoimidazol-2-yl)-2-hydroxy-1*S*-phenyethylethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1*S*-[2-(4,5-dihydro-4*S*-phenyloxazol-2-yl)-2-hydroxy-1*S*-phenethylethyl-carbamoyl]-3-methylbutylcarbamate;
- 15 benzyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1-[2-(4,5-dihydro-5-phenyloxazol-2-yl)-2-hydroxy-1-phenethylethylcarbamoyl]-3-methylbutylcarbamate;
- 20 benzyl 1-[2-(4,5-dihydro-4*S*-methyl-5*S*-phenyloxazol-2-yl)-2-hydroxy-1-phenyethyl-carbamoyl]-3-methylbutylcarbamate;
- benzyl 3-methyl-1-(2-hydroxy-2-naphtho[2,3-d]oxazol-2-yl-1-phenethylethylcarbamoyl)-butylcarbamate;
- benzyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-methylpropylcarbamate;
- 25 benzyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1*S*-[2-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-2-hydroxy-1*S*-phenethylethyl-carbamoyl]-3-methylbutylcarbamate;
- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenyl-30 butyl]-4,5-dihydrooxazole-4-carboxylate;
- methyl 2-[2-(2,2-dimethylpropionylamino)-4-phenylbutyryl]oxazole-4-carboxylate;
- tert*-butyl 4-{1*S*-[2-(5-*tert*-butylbenzoxazol-2-yl)-2-hydroxy-1*S*-phenethylethyl-

- carbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
tert-butyl 4-{1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-sulfamoylbenzooxazol-2-yl)ethylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
tert-butyl 4-[1*S*-(2-hydroxy-2-naphtho[1,2-d]oxazol-2-yl)-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamoyl)piperidine-1-carboxylate;
5 *tert*-butyl 4-[1*S*-(2-hydroxy-2-naphtho[2,1-d]oxazol-2-yl)-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamoyl)piperidine-1-carboxylate;
10 *tert*-butyl 4-{1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenylbenzooxazol-2-yl)ethylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
15 *tert*-butyl 4-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-methylbutylcarbamoyl)piperidine-1-carboxylate;
20 *tert*-butyl 3-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-methylbutylcarbamoyl]benzylcarbamate;
25 *tert*-butyl 4-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-cyclohexylethylcarbamoyl)piperidine-1-carboxylate;
30 benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylcarbamoyl]-2-methylbutylcarbamate;
35 pyridin-3-yl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylcarbamoyl] butylcarbamate;
40 benzyl 1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylsulfamoylmethyl]-2*R*-methylbutylcarbamate;
45 benzyl 3-methyl-1*S*-(1*S*-pyridin-2-ylcarbonyl-3-phenylpropylcarbamoyl)butylcarbamate;
50 benzyl 1-[1-(pyridin-3-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
55 benzyl 1-[1-(quinolin-3-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
60 benzyl 1-[1-(1*H*-indol-5-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
65 benzyl 1-[1-(benzofuran-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
70 benzyl 1-[1-(benzothiazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
75 benzyl 3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butylcarbamate;
80 *N*-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butyl]-4-methylpiperazine-1-carboxamide;

- tert-butyl 4-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butylcarbamoyl]piperazine-1-carboxylate;
- benzyl 3-methyl-1*S*-(3-phenyl-1*S*-thien-2-ylcarbonylpropylcarbamoyl)butylcarbamate;
- benzyl 1*S*-[1*S*-(1-methyl-1*H*-imidazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-methyl-
5 butylcarbamate;
- benzyl 1*S*-(1*S*-thiazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylpropylcarbamate;
- N-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butyl]piperazine-1-carboxamide;
- benzyl 1*S*-[1*S*-(4-methylthiazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutyl-
10 carbamate;
- benzyl 1*S*-(1*S*-furan-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1*S*-[1*S*-(1-benzyl-1*H*-imidazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-methyl-
butylcarbamate;
- benzyl 3-phenyl-1-(4,5-dihydro-4*S*-phenyloxazol-2-ylcarbonyl)propylcarbamate;
- benzyl 3-phenyl-1-(4,5-dihydro-5-phenyloxazol-2-ylcarbonylpropylcarbamate;
- benzyl [1-(4,5-dihydro-4*S*-methyl-5*S*-phenyloxazol-2-ylcarbonyl)-3-phenylpropyl]-
carbamate;
- ethyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]thiazole-4-
carboxylate;
- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenyl-
butyl]oxazole-4-carboxylate;
20 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenylbutyl]-
oxazole-4-carboxylic acid;
- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-phenylcarbamoyloxazol-2-yl)ethyl-
25 carbamoyl]butylcarbamate;
- benzyl 1-[2-(4-benzylcarbamoyloxazol-2-yl)-2-hydroxy-1-phenethylethylcarbamoyl]-3-
methylbutylcarbamate;
- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-phenyethylcarbamoyloxazol-2-yl)ethyl-
carbamoyl]butylcarbamate;
- benzyl 1-[1-(4,5-dihydro-4*S*-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-
30 methylbutylcarbamate;
- benzyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-pentylcarbamoyl)-3-methylbutylcarbamate;

- benzyl 1*S*-[1*S*-(4,5-dihydrooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- N*-[3-methyl-1*S*-(3-phenyl-1*S*-benzooxazol-2-ylcarbonylpropylcarbamoyl)butyl]-piperidine-4-carboxamide;
- 5 benzyl 1-[1-(4,5-dihydro-5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(4,5-dihydro-5*S*-phenyl-4*S*-methyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 10 benzyl 1*S*-(1*S*-phenethyl-2-benzimidazol-2-yl-1-oxoethylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1-[1-(naphtho[2,3-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]-4,5-dihydrooxazole-4-carboxylate;
- 15 benzyl 1*S*-[1*S*-(4,5-dihydro-4,4-dimethyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylpropylcarbamate;
- benzyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylbutylcarbamate;
- 20 benzyl 1*S*-[1*S*-(5-chlorobenzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- N*-{3-methyl-1*S*-[3-phenyl-1*S*-(5-chlorobenzooxazol-2-ylcarbonyl)propylcarbamoyl]-butyl}piperidine-4-carboxamide;
- 25 *N*-[2-cyclohexyl-1*S*-(3-phenyl-1*S*-benzooxazol-2-ylcarbonylpropylcarbamoyl)ethyl]-piperidine-4-carboxamide;
- methyl 2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryloxazole-4-carboxylate;
- benzyl 1-[1-(4-phenylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-
- 30 methylbutylcarbamate;
- benzyl 1-[1-(4-benzylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

- 5 *tert*-butyl 4{1*S*-[1*S*-(5-*tert*-butylbenzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- 10 *tert*-butyl 4-{1*S*-[1*S*-(5-sulfamoylbenzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- 15 *N*-(3-methyl-1*S*-[3-phenyl-1*S*-(5-*tert*-butylbenzoxazol-2-ylcarbonyl)propylcarbamoyl]butyl)piperidine-4-carboxamide;
- 20 *N*-(3-methyl-1*S*-[1*S*-(5-sulfamoylbenzoxazol-2-ylcarbonyl)propylcarbamoyl]-butyl)piperidine-4-carboxamide;
- 25 *tert*-butyl 4-[1*S*-(1*S*-naphtho[1,2-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl]piperidine-1-carboxylate;
- 30 *tert*-butyl 4-[1*S*-(1*S*-naphtho[2,1-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl]piperidine-1-carboxylate;
- 35 *N*-(3-methyl-1*S*-[3-phenyl-1*S*-(5-phenylbenzoxazol-2-ylcarbonyl)propylcarbamoyl]-butyl)piperidine-4-carboxamide;
- 40 *N*-(3-methyl-1*S*-[3-phenyl-1*S*-(naphtho[2,1-d]benzoxazol-2-ylcarbonyl)propylcarbamoyl]butyl)piperidine-4-carboxamide;
- 45 *N*-(3-methyl-1-[3-phenyl-1-(5-phenylbenzoxazol-2-ylcarbonyl)propylcarbamoyl]-butyl)piperidine-4-carboxamide;
- 50 benzyl 1-[1-(4-phenyethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 55 benzyl 1-{1-[4-(3-phenylpropylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 60 *tert*-butyl 4-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-2-methylbutylcarbamoyl]piperidine-1-carboxylate;
- 65 *tert*-butyl 3-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-2-methylbutylcarbamoyl]benzylcarbamate;
- 70 *N*-[2-methyl-1*S*-(3-phenyl-1*S*-benzoxazol-2-ylcarbonylpropylcarbamoyl)butyl]-piperidine-4-carboxamide;
- 75 *N*-[2-methyl-1*S*-(3-phenyl-1*S*-benzoxazol-2-ylcarbonylpropylcarbamoyl)butyl]-3-aminomethylbenzamide;

benzyl 1-[1-[4-(2-indol-3-ylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 1-[1-(4-methylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

5 benzyl 2-{2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]-oxazol-2-ylcarbonylamino}valerate;

benzyl 1S-[1S-[4-(4-benzylpiperidin-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

10 benzyl 1S-[1S-(4-furan-2-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 3-methyl-1S-[1S-(4-pyridin-2-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;

benzyl 3-methyl-1S-[1S-(4-pyridin-3-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;

15 benzyl 3-methyl-1S-[1S-(4-pyridin-4-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;

benzyl 1S-[1S-[4-(2-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 1S-[1S-[4-(3-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

20 benzyl 1S-[1S-[4-(4-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 3-methyl-1S-[1S-(4-diphenylmethyldiacetamido-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

25 benzyl 1S-[1S-(4-adamantan-1-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 1-[1-[4-(1-methylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

benzyl 1-[1-[4-(1S-phenylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

30 benzyl 1-[1-[4-(1R-phenylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

- benzyl 1-[1-[4-(*N*-benzyl-*N*-methylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(4-pyrrolidin-1-ylcarbonyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 5 benzyl 1-[1-(4-piperidin-1-ylcarbonyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-[4-(2,3-dihydroindol-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-[4-(3,4-dihydro-1*H*-isoquinolin-2-ylcarbonyl)oxazol-2-ylcarbonyl]-3-
- 10 phenylpropylcarbamoyl]-3-methyl;
- benzyl 1-[1-[4-(3,4-dihydro-2*H*-quinolin-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(4-naphth-1-ylmethylcarbonyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 15 *tert*-butyl 4-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-2-cyclohexylethylcarbamoyl]piperidine-1-carboxylate;
- 1*S*-{1*S*-[4-(3,4-dihydro-2*H*-quinol-1-ylcarbonyl)oxazol-2-ylcarbonyl]-ethylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 3-methyl-1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-
- 20 butylcarbamate;
- pyridin-3-yl 3-methyl-1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-butylcarbamate;
- benzyl 1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylsulfamoylmethyl]-2*R*-methylbutylcarbamate;
- 25 benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(3-phenylpropylcarbamoyl)oxazol-2-yl]-ethylcarbamoyl}butylcarbamate;
- benzyl 1-{2-hydroxy-2-[4-(2-indol-3-ylethylcarbamoyl)oxazol-2-yl]-1-phenethylethylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 3-methyl-1-[2-hydroxy-2-(4-methylcarbonyloxazol-2-yl)-1-phenethylethyl-
- 30 carbamoyl]butylcarbamate;
- benzyl 2-{2-[2-(2-benzyloxycarbonylamino-4-methylvalerylanino)-1-hydroxy-4-phenylbutyl]oxazol-2-ylcarbonylamino}valerate;

- benzyl 1*S*-{2-[4-(4-benzylpiperidin-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethyl-ethylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 1*S*-[2-(4-furan-2-ylmethylcarbamoyloxazol-2-yl)-2-hydroxy-1*S*-phenethylethyl-carbamoyl]-3-methylbutylcarbamate;
- 5 benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-2-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-3-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-4-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- 10 benzyl 3-methyl-1*S*-{2-[4-(2-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1*S*-{2-[4-(3-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- 15 benzyl 3-methyl-1*S*-{2-[4-(4-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1*S*-{2-hydroxy-1*S*-phenethyl-2-[4-(2*R*-phenylcycloprop-1*S*-yl-carbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;
- benzyl 1*S*-[2-(4-adamantan-1-ylmethylcarbamoyloxazol-2-yl)-2-hydroxy-methyl]-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamate;
- 20 benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-diphenylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1-{2-hydroxy-2-[4-(1-methylethylcarbamoyl)oxazol-2-yl]-1-phenethylethylcarbamoyl}butylcarbamate;
- 25 benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(2*S*-phenyethylcarbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(2*R*-phenyethylcarbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(*N*-benzyl-*N*-methylcarbamoyl)oxazol-2-yl]-2-hydroxy-1-phenethylethylcarbamoyl}butylcarbamate;
- 30 benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-pyrrolidin-1-ylcarbonyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;

-
- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-piperidin-1-ylcarbonyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(2,3-dihydroindol-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylethylcarbamoyl}butylcarbamate;
- 5 benzyl 3-methyl-1-{2-[4-(3,4-dihydro-1H-isoquinolin-2-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(3,4-dihydro-1H-isoquinolin-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-[2-hydroxy-2-(4-naphth-1-ylmethylcarbonyloxazol-2-yl)-1-phenethylethylcarbamoyl]butylcarbamate;
- 10 benzyl 1*S*-{2-[4-(3,4-dihydro-2*H*-quinol-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1*S*-methylethylcarbamoyl}-3-methylbutylcarbamate;
- N*-[3-methyl-1*S*-(1*S*-thiazol-2-ylcarbonylethylcarbamoyl)butyl]-4-morpholin-4-ylbenzamide;
- 15 *N*-[1*S*-(2-benzoazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-3-methylbutyl]-4-(4-methylpiperazin-1-yl)benzamide;
- N*-[1*R*-(1*S*-benzoazol-2-yl-carbonylprop-1-ylcarbamoyl)-2-(2-methylprop-1-ylsulfonyl)ethyl]morpholine-4-carboxamide;
- N*-[1*R*-(1*S*-benzoazol-2-yl-carbonylprop-1-ylcarbamoyl)-2-cyclopropylmethylsulfonyl-20 ethyl]morpholine-4-carboxamide;
- N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-nicotinamide;
- N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-isonicotinamide;
- 25 pyridine-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-ethyl}-amide;
- pyrazine-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-ethyl}-amide;
- N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-30 ethyl}-6-hydroxynicotinamide;
- 2-amino-*N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}-nicotinamide;

- 6-amino- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -nicotinamide;
- 3-hydroxypyridine-2-carboxylic acid- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ amide;
- 5 morpholine-4-carboxylic acid- $\{(R)\text{-}1\text{-}(4\text{-cyanotetrahydropyran-4\text{-}ylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ amide;
- morpholine-4-carboxylic acid- $\{(R)\text{-}1\text{-}(4\text{-cyano-1-methylpiperidin-4\text{-}ylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ amide;
- (R)-N-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(3, 3-
- 10 dimethylureido)propionamide;
- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ carbamic acid allyl ester;
- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -carbamic acid isopropyl ester;
- 15 $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -carbamic acid isobutyl ester;
- N- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -3,4-difluorobenzamide;
- 20 N- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -3-methylbenzamide;
- thiophene-2-carboxylic acid- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ amide;
- 25 4-bromo-N- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{-phenylmethane-sulfonyl}\text{]}\text{-}ethyl\}$ benzamide;
- N- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{phenylmethanesulfonyl}\text{]}\text{-}ethyl\}$ -4-trifluoromethoxybenzamide;
- naphthalene-2-carboxylic acid- $\{(R)\text{-}1\text{-}(cyanomethylcarbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoro-$
- 30 methoxy)phenylmethanesulfonyl]ethyl} amide;
- (E)-N- $\{(R)\text{-}1\text{-}(cyanomethyl-carbamoyl)\text{-}2\text{-}[2\text{-}(1,1\text{-}difluoromethoxy)\text{-phenylmethane-sulfonyl}\text{]}\text{-}ethyl\}$ -3-phenylacrylamide;

- 5-methyl-thiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- biphenyl-4-carboxylic acid- $\{(R)\text{-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 5 1H-indole-5-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- benzo[1,3]dioxole-5-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 10 benzo[b]thiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -amide;
- N- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -3-phenoxybenzamide;
- quinoline-3-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 15 N- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -3-(1-phenylmethanoyl)benzamide;
- 4-chloro-N- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -3-fluoro-4-methoxybenzamide;
- 20 N- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -3-bromo-thiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 3-chlorobenzo[b]thiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 25 3-chlorothiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- N- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -trifluoromethyl-benzamide;
- (R)-N-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(naphthalene-30 2-sulfonylamino)-propionamide;
- cyclopentanecarboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;

- N-[1R-cyanomethylcarbamoyl-2-(3-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
N-(1R-cyanomethylcarbamoyl-2-(3-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
- 5 N-[1R-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1R-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-morpholine-4-carboxamide;
- 10 N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;
- N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)-butyl]-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethylbenzylsulfonylmethyl)propionamide;
- 15 N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)pentyl]-4-(2-methoxybenzenesulfonyl)-2-[2-(2-methoxybenzenesulfonyl)ethyl]butyramide;
- 4-benzenesulfonyl-2-(2-benzenesulfonylethyl)-N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)-butyl]butyramide;
- 20 (R)-N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-cyclohexylmethyl-3-benzylsulfonyl-propionamide;
- N-[(S)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-cyclohexyl-2-cyclohexylmethyl-propionamide;
- 25 N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-isobutylsulfanyl-2-isobutylsulfanyl-methylpropionamide;
- N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanyl-methylpropionamide;
- 30 N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)-butyl]-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)butyramide;
- N-cyanomethyl-4-morpholin-4-yl-4-oxo-2-(2-trifluoromethylbenzylsulfonylmethyl)-butyramide;
- N⁴-(4-carbamoyl-phenyl)-N¹-cyanomethyl-2-benzylsulfonylmethylsuccinamide;

N-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-4-morpholin-4-yl-4-oxobutyramide;

5 N-[(S)-1-(1-benzooxazol-2-ylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;

(S)-2,2-difluoro-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutanoylamino)-3-oxo-hexanoic acid dimethylamide;

10 N-[(S)-1-(1-benzylcarbamoylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;

3-biphenyl-3-yl-N-cyanomethyl-2-benzylsulfonylmethylpropionamide;

3-biphenyl-4-yl-N-cyanomethyl-2-benzylsulfonylmethylpropionamide;

3-(3-bromo-phenyl)-N-cyanomethyl-2-benzylsulfonylmethylpropionamide;

15 N-[(S)-1-((E)-2-benzenesulfonylvinyl)pentyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;

N-(3-benzenesulfonyl-1-phenethylallyl)-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;

N-cyanomethyl-3-(3-cyanobenzylsulfonyl)-2-benzylsulfonylmethylpropionamide;

4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-{(S)-1-[1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanoyl]-propyl}-butyramide;

20 N-cyanomethyl-2-[2-1,1-difluoromethoxy)benzylsulfanyl methyl]-3-benzylsulfanyl-propionamide;

N-cyanomethyl-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfanyl methyl)-propionamide;

25 N-cyanomethyl-3-isobutylsulfanyl-2-isobutylsulfanyl methylpropionamide;

N-cyanomethyl-4-phenylsulfanyl-2-(2-phenylsulfanylethyl)butyramide;

N-cyanomethyl-3-[2-(1,1-difluoromethoxy)benzylsulfanyl]-2-[2-(1,1-difluoromethoxy)-benzylsulfanyl methyl]propionamide;

30 3-benzylsulfanyl-2-benzylsulfanyl methyl-N-cyanomethylpropionamide;

N-cyanomethyl-2-[2-1,1-difluoromethoxy)benzylsulfanyl methyl]-3-benzylsulfanyl-propionamide;

N-cyanomethyl-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethyl-

- benzylsulfonylmethyl)propionamide;
- 4-benzenesulfonyl-2-(2-benzenesulfonylethyl)-*N*-cyanomethylbutyramide;
- N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)benzylsulfonyl]-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]propionamide;
- 5 *N*-cyanomethyl-3-benzylsulfonyl-2-benzylsulfonylmethylpropionamide;
- N*-[(*S*)-1-(1-benzylcarbamoylmethanoyl)propyl]-3-benzylsulfonyl-2-benzylsulfonylmethylpropionamide;
- N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-3-benzylsulfonylpropionamide;
- 10 *N*-cyanomethyl-3-(2-methylpropane-1-sulfonyl)-2-(2-methylpropane-1-sulfonylmethyl)propionamide;
- acetic acid (2*S*,3*S*)-3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutanoylamino)-4-oxo-azetidin-2-yl ester;
- N*-cyanomethyl-3-(2-methylthiazol-4-ylmethylsulfonyl)-2-benzylsulfonylmethyl-
- 15 propionamide;
- N*-(3-benzenesulfonylamino-2-oxopropyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 3-biphenyl-3-yl-*N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]propionamide;
- 20 (3'-{2-(cyanomethylcarbamoyl)-3-[2-(1,1-difluoromethoxy)benzylsulfonyl]propyl}-biphenyl-4-yl)-carbamic acid ethyl ester;
- N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-3-(4'-methylsulfonylaminobiphenyl-3-yl)propionamide;
- 3-(3-bromophenyl)-*N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)phenyl-
- 25 methylsulfonylmethyl]-propionamide;
- N*-cyanomethyl-2-((E)-3-phenyl-allyl)-3-benzylsulfonylpropionamide;
- N*-cyanomethyl-3-benzylsulfonyl-2-(3-phenylpropyl)propionamide;
- 4-morpholin-4-yl-4-oxo-*N*-(1-(2-oxo-2-phenylacetyl)pentyl)-2-benzylsulfonylmethylbutyramide;
- 30 4-morpholin-4-yl-4-oxo-*N*-(1-(oxophenylacetyl)pentyl)-2-benzylsulfonylmethylbutyramide as a mixture of diastereomers;

- 3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester;
- 4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester;
- 5 *N*-(1,1-dimethyl-2-oxazolo[4,5-*b*]pyridin-2-yl-2-oxoethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;
- 10 *N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide;
- N*-[1-(5-methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 15 *N*-[1-(5-methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;
- N*-[1-(5-methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide;
- 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-(1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl)butyramide;
- 20 4-oxo-2-benzylsulfonylmethyl-*N*-(1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl)-4-piperidin-1-ylbutyramide;
- 4-oxo-2-benzylsulfonylmethyl-*N*-(1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl)-4-pyrrolidin-1-yl-butyramide;
- 25 4-morpholin-4-yl-*N*-(1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propyl)-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;
- N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-ylbutyramide;
- 30 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-(1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)propyl)butyramide;

- 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-ylbutyramide;
- 5 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- N*-[1-(benzooxazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-ylbutyramide;
- N*-[1-(benzooxazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-ylbutyramide;
- 10 *N*-[1-(benzooxazole-2-carbonyl)propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide;
- 2-cyclohexylmethyl-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)propyl]-4-oxobutyramide;
- 15 2-cyclohexylmethyl-*N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-morpholin-4-yl-4-oxo-butyramide;
- N*-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- N*-[1-(benzooxazole-2-carbonyl)propyl]-2-(2-cyclohexylethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- 20 2-(2-cyclohexylethyl)-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide;
- 2-(2-cyclohexylethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 25 2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 2-(2-difluoromethoxybenzylsulfonylmethyl)-*N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide;
- N*-[1-(benzooxazole-2-carbonyl)propyl]-2-(2-difluoromethoxybenzylsulfonylmethyl)-4-
- 30 morpholin-4-yl-4-oxo-butyramide;
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid, 1-(benzooxazole-2-carbonyl)propyl]amide;

- (*R*)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(*S*)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)propyl]butyramide;
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid, (*S*)-1-(5-phenyl-[1,2,4]oxadiazole-3-carbonyl)propyl]amide;
- 5 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[(*S*)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)propyl]butyramide;
- (*R*)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(*S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]butyramide;
- 10 4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-(1,1-dimethyl-2-oxazol-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 15 *N*-4-isopropyl-*N*-1-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-2-benzylsulfonylmethylsuccinamide;
- 2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-butyramide;
- 2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-butyramide;
- 20 2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-butyramide;
- N*-[1-(benzooxazole-2-carbonyl)butyl]-2-benzylsulfonyl-3-(tetrahydropyran-4-yl-oxymethyl)-propionamide;
- 25 *N*-[1-(benzooxazole-2-carbonyl)butyl]-3-ethanesulfonyl-2-(tetrahydropyran-4-yl-oxymethyl)-propionamide;
- N*-(1-benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide;
- 2-cyclopropylmethylsulfonylmethyl-*N*-{(*S*)-1-[(*R*)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propyl}-4-morpholin-4-yl-4-oxo-butyramide;
- 30 *N*-{(*S*)-1-[(*R*)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propyl}-2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid
{(*S*)-1-[(*R*)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propyl} amide;

- 2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-N-[*(S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]butyramide;
- 2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[*(S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]butyramide;
- 5 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid,
(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl} amide;
- 10 3-hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-azepane-1-carboxylic acid *tert*-butyl ester;
- 15 4-(2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-hydroxy-azepane-1-carboxylic acid *tert*-butyl ester;
- 20 3-hydroxy-4-[2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-azepane-1-carboxylic acid *tert*-butyl ester;
- 25 4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid *tert*-butyl ester;
- 30 4-(2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-oxo-azepane-1-carboxylic acid *tert*-butyl ester;
- 4-[2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-3-oxo-azepane-1-carboxylic acid *tert*-butyl ester;
- N*-(1-benzenesulfonyl-3-oxo-azepan-4-yl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-(1-benzenesulfonyl-3-oxo-azepan-4-yl)-2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- N*-[(1*S*)-1-(benzoxazol-2-ylhydroxymethyl)-3-phenylpropyl]-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide;
- (*R*)-2-((*S*)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid, 1-(benzoxazole-2-carbonyl)propyl]-amide;
- (*R*)-5-(2-difluoromethoxyphenyl)-2-((*S*)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide;
- 4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)cyclopropyl]-4-oxo-2-benzylsulfonylmethyl -
- 35 butyramide;
- (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonylpropionamide;

- (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide;
- (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoromethoxy)phenylmethane-sulfonyl]-2-hydroxypropionamide;
- 5 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-hydroxy-propionamide;
- morpholine-4-carboxylic acid (*R*)-1-(cyanomethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester;
- 10 morpholine-4-carboxylic acid (*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]ethyl ester;
- (*R*)-(2-methoxyethyl)-carbamic acid 1-(cyanomethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester;
- 15 (*S*)-diethylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-pyrrolidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-morpholine-4-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-4-ethyl-piperazine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- 20 (*S*)-2-hydroxymethylpyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-ethyl ester;
- (*S*)-(2,2,2-trifluoroethyl)carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-(2-hydroxyethyl)carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (tetrahydrofuran-2-ylmethyl)carbamic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-ethyl ester;
- 25 (*S*)-azetidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-cyclopropylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-piperidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-(2-methoxyethyl)-carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*R*)-3-hydroxypyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-ethyl ester;
- 30 (*S*)-3-hydroxypyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-ethyl ester;
- (*S*)-morpholine-4-carboxylic acid 1-(cyanomethylcarbamoyl)-3-cyclohexylpropyl ester;

- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
- 5 morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propylcarbamoyl]-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl ester;
- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzothiazol-2-ylmethanoyl)propylcarbamoyl]-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl ester;
- 10 pyrrolidine-1-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
- dimethyl-carbamic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- 15 morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzylcarbamoylmethanoyl)propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- morpholine-4-carboxylic acid (*S*)-1-[*(S)*-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- 20 morpholine-4-carboxylic acid (*S*)-1-[*(S)*-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- (*S*)-2-{(*R*)-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-hydroxy-propanoyl-amino}-*N*-methoxy-*N*-methylbutyramide;
- (*R*)-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-*N*-((*S*)-1-formylpropyl)-2-hydroxy-propionamide;
- 25 (*R*)-*N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propyl]-2-hydroxy-3-phenylmethane-sulfonylpropionamide;
- (*S*)-3-{3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]propanoylamino}-2-oxo-pentanoic acid benzylamide;
- 30 *N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-propyl]-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-propionamide;
- N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-3-phenylpropyl]-3-*p*-tolylmethanesulfonyl-propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)propionamide;
- 35 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)propionamide;

- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-1*H*-thiomorpholin-4-yl)-1-ethyl-2,3-dioxopropyl]propionamide;
- 5 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methylsulfonylpiperazin-1-yl)-2,3-dioxopropyl]propionamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid dimethylamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide;
- 10 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid phenylamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide;
- 15 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)amide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)amide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-ylethyl)amide;
- 20 (*R*)-*N*-[(*S*)-1-(1-benzoazol-2-ylmethanoyl)propyl]-2-(2-nitrophenylamino)-3-phenylmethanesulfonylpropionamide;
- N*-[1-(benzoazole-2-carbonyl)propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-yl-amino)-propionamide.
- 25 (*R*)-*N*-[(*S*)-1-(1-benzoazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide;
- (2*S*) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(*S*)-cyano-3-phenyl-propyl)-amide;
- N*-(1(*S*)-cyano-3-phenyl-propyl)-2-(*S*)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenylbutyramide;
- 30 *N*-(1-(*S*)-cyano-3-phenylpropyl)-2-(*S*)-fluoro-4-phenylbutyramide;
- N*-(1-(*S*)-cyano-3-phenylpropyl)-2,2-difluoro-4-phenylbutyramide;

- N-(1-(*S*)-cyano-3-phenylpropyl)-2-(*S*)-hydroxy-4-phenylbutyramide;
N-(1-(*S*)-cyano-3-phenylpropyl)-2-(*R*)-hydroxy-4-phenylbutyramide;
N-(1-(*S*)-cyano-3-phenylpropyl)-2-(*R*)-methoxy-4-phenylbutyramide;
2,2-difluoro-5-phenylpentanoic acid (1-cyanocyclopropyl)-amide;
5 N-(1-(*S*)-cyano-3-phenylpropyl)-4-phenylbutyramide;
2,2-difluoro-5-phenylpentanoic acid ((*S*)-1-cyano-3-phenylpropyl)amide;
N-(4-cyano-1-ethylpiperidin-4-yl)-3-cyclohexylpropionamide;
N-(4-cyano-1-ethylpiperidin-4-yl)-3-(2-difluoromethoxyphenylmethanesulfonyl)-
propionamide;
10 (*S*)-*tert*-butylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
(*R*)-carbamic acid 1-(cyanomethylcarbamoyl)-2-(2-difluoromethoxy-
phenylmethanesulfonyl)ethyl ester;
(*S*)-carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
(*R*)-morpholine-4-carboxylic acid 1-(1-cyanocyclopropylcarbamoyl)-2-
15 phenylmethanesulfonylethyl ester;
(*R*)-morpholine-4-carboxylic acid 1-(4-cyanotetrahydropyran-4-ylcarbamoyl)-2-
phenylmethanesulfonylethyl ester;
3-cyclohexyl-2-hydroxy-N-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propyl]propionamide;
(*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-2-isopropylamino-3-phenylmethanesulfonyl-
20 propionamide;
R-*N*-[1-(benzothiazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-
4-ylamino)propionamide;
(*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-
propionamide;
25 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-dimethylamino-3-phenylmethanesulfonyl-
propionamide;
(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-
pyran-4-ylamino)propionamide;
(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(1-methylpiperidin-4-ylamino)-3-
30 phenylmethanesulfonylpropionamide;
(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(bis-thiophen-2-ylmethylamino)-3-
phenylmethanesulfonylpropionamide;

- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-dibenzylamino-3-phenylmethanesulfonylpropionamide;
- (*S*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(tetrahydropyran-4-ylamino)-3-thiophen-2-ylpropionamide;
- 5 (*S*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-isopropylamino-3-thiophen-2-ylpropionamide;
- (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 10 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-
pyran-4-ylamino)propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-isopropylamino-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-[(2-methoxyethyl)-(tetrahydropyran-4-yl)-
amino]-3-phenylmethanesulfonylpropionamide;
- 15 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethane-
sulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-dimethylamino-3-phenylmethanesulfonyl-
propionamide;
- (*1S*)-*N*-[1-(benzooxazole-2-carbonyl)butyl]-2-(*S*)-fluoro-4-phenylbutyramide;
- 20 2,2-difluoro-5-phenylpentanoic acid [(*S*)-1-(benzoxazole-2-carbonyl)butyl]amide;
 morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(benzooxazole-2-carbonyl)propylcarbamoyl]-2-
cyclohexyl-ethyl ester;
- morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(oxazolo[4,5-b]pyridine-2-
carbonyl)propylcarbamoyl]ethyl ester;
- 25 morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-
carbonyl)propylcarbamoyl]ethyl ester;
- morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(5-phenyl-[1,3,4]oxadiazole-2-
carbonyl)propylcarbamoyl]ethyl ester;
- morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(benzooxazole-2-carbonyl)propylcarbamoyl]-3-
- 30 cyclohexylpropyl ester;
 4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)pentanoylamino]-3-oxo-azepane-1-
carboxylic acid benzyl ester;

- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethane-sulfonylpropionamide;
- 5 (*R*)-*N*-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethane-sulfonylpropionamide;
- (*R*)-3-phenylmethanesulfonyl-*N*-[(*S*)-3-phenyl-1-(thiazole-2-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-3-phenylpropyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 10 (*R*)-3-cyclopropylmethanesulfonyl-*N*-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-3-phenylmethanesulfonyl-*N*-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- 15 (*R*)-*N*-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- {(*R*)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- 20 {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethane-sulfonylethyl} carbamic acid *tert*-butyl ester;
- {(*S*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-thiophen-2-ylethyl}-carbamic acid *tert*-butyl ester;
- 25 {(*R*)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethane-sulfonylethyl} carbamic acid *tert*-butyl ester;
- (*R*)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propylcarbamoyl}-2-phenylmethanesulfonylethyl)-carbamic acid *tert*-butyl ester;
- 30 ((*R*)-2-cyclopropylmethanesulfonyl-1-{(*S*)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)hydroxy-methyl]propylcarbamoyl} ethyl) carbamic acid *tert*-butyl ester;

- {(R)-1-[1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxymethyl)-3-phenylpropylcarbamoyl]-2-cyclopropylmethanesulfonylethyl}-carbamic acid *tert*-butyl ester;
- 5 {(R)-1-[(S)-1-(hydroxythiazol-2-ylmethyl)-3-phenylpropylcarbamoyl]-2-phenylmethane-sulfonyl-ethyl}-carbamic acid *tert*-butyl ester;
- {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-cyclopropylmethane-sulfonylethyl}-carbamic acid *tert*-butyl ester;
- 10 (R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propylcarbamoyl}-2-phenyl-methanesulfonylethyl)carbamic acid *tert*-butyl ester;
- ((R)-2-cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]propylcarbamoyl}ethyl)carbamic acid *tert*-butyl ester;
- {(R)-1-[1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- 15 {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxymethyl)-3-phenylpropylcarbamoyl]-2-cyclopropylmethanesulfonylethyl}-carbamic acid *tert*-butyl ester;
- {(R)-1-[(S)-1-(hydroxythiazol-2-yl-methyl)-3-phenylpropylcarbamoyl]-2-phenylmethane-sulfonylethyl} carbamic acid *tert*-butyl ester;
- (R)-2-phenylmethanesulfonyl-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)hydroxy-20 methyl]propylcarbamoyl}ethyl)carbamic acid *tert*-butyl ester;
- (R)-N-[1-(benzoxazole-2-carbonyl)butyl]-2-[cyclopropylmethyl(tetrahydropyran-4-ylmethyl)amino]-3-phenylmethanesulfonylpropionamide;
- (R)-N-[1-(benzothiazol-2-yl-hydroxymethyl)butyl]-2-dibenzylamino-3-phenylmethane-sulfonylpropionamide;
- 25 (R)-N-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)propionamide;
- (R)-N-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-2-isopropylamino-3-phenylmethane-sulfonyl-propionamide;
- (R)-N-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-2-dimethylamino-3-phenylmethane-30 sulfonyl-propionamide;
- (R)-N-[(S)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;

- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-yl-hydroxymethyl)butyl]-2-(1-methylpiperidin-4-ylamino)-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-(bis-thiophen-2-ylmethylamino)-3-phenylmethanesulfonylpropionamide;
- 5 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-dibenzylamino-3-phenylmethane-sulfonylpropionamide;
- (*S*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-(tetrahydropyran-4-ylamino)-3-thiophen-2-yl-propionamide;
- 10 (*S*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-yl-hydroxymethyl)butyl]-2-isopropylamino-3-phenylmethane-sulfonylpropionamide;
- (*R*)-*N*-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 15 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)-propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-[(2-methoxyethyl)-(tetrahydro-20 pyran-4-yl)amino]-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-cyclohexylamino-3-phenyl-methanesulfonyl-propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-dimethylamino-3-phenylmethane-sulfonyl-propionamide;
- 25 *N*-cyanomethyl-3-cyclohexylpropionamide;
- N*-cyanomethyl-3-(2-difluoromethoxyphenylmethanesulfonyl)propionamide;
- 3-(3-cyclohexylpropionylamino)-2-oxo-5-phenylpentanoic acid thiazol-2-ylamide;
- 3-cyclohexyl-*N*-(1-formyl-3-phenylpropyl)propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-30 carbonyl)propyl]propionamide;
- N*-[(*S*)-1-(benzooxazole-2-carbonyl)propyl]-2-(2-cyanophenylamino)-3-cyclohexyl-propionamide;

- N-Cyanomethyl-3-cyclohexyl-2-(4-methoxyphenoxy)propionamide;
- 2-benzyloxy-N-cyanomethyl-3-cyclohexylpropionamide;
- (R)-N-[(S)-1-(1-benzoxazol-2-ylmethanoyl)butyl]-2-benzyloxy-3-phenylmethane-sulfonylpropionamide;
- 5 (R)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenyl-methanesulfonylpropionamide;
- (S)-N-[(S)-1-(1-benzoxazol-2-ylmethanoyl)butyl]-2-hydroxy-3-phenylpropionamide;
- (R)-N-[(S)-1-(1-benzoxazol-2-ylmethanoyl)propyl]-3-phenylmethanesulfonyl-2-triisopropylsilyloxypropionamide;
- 10 (R)-N-[(S)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide;
- (R)-2-hydroxy-3-phenylmethanesulfonyl-N-[(S)-1-(1-pyridazin-3-ylmethanoyl)butyl]-propionamide;
- (S)-3-((R)-2-hydroxy-3-phenylmethanesulfonylpropanoylamino)-2-oxo-pentanoic acid
- 15 benzylamide;
- (R)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)propyl]-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-hydroxypropionamide;
- (R)-N-[(S)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-hydroxypropionamide;
- 20 (2R,5S)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-morpholin-3-one;
- (S)-N-[(S)-1-(benzoxazol-2-ylcarbonyl)-propyl]-3-cyclohexyl-2-(1,1-dioxo-benzo[d]isothiazol-3-ylamino)propionamide;
- 2-(1,1-dioxobenzo[d]isothiazol-3-ylamino)-4-methyl-pentanoic acid [1-(benzoxazol-2-ylcarbonyl)propyl]amide;
- 25 (S)-4-methyl-2-(3-oxo-3H-isoindol-1-ylamino)-pentanoic acid (S)-[1-(benzoxazol-2-ylcarbonyl)propyl]amide;
- ({1(S)}-{1(S)}-benzoxazol-2-ylcarbonyl)propylcarbamoyl]-3-methylbutylamino}-morpholin-4-ylmethylene)carbamic acid ethyl ester;
- 30 N-[1-(benzoxazol-2-yl-hydroxy-methyl)-propyl]-3-cyclohexyl-2-{{[N-(2,2,2-trifluoroethyl)-morpholine-4-carboximidoyl]-amino}-propionamide};

- N-[1(S)-(benzoxazol-2-ylcarbonyl)-propyl]-3-phenylmethanesulfonyl-2(R)-{[N-(2,2,2-trifluoroethyl)-morpholin-4-ylcarboximidoyl]amino}propionamide;
- N-[1-(benzoxazol-2-ylcarbonyl)propyl]-3-cyclohexyl-2(S)-[N-(2,2,2-trifluoroethyl)-formimidoylamino]propionamide;
- 5 N-[1-(benzoxazol-2-ylcarbonyl)propyl]-3-cyclohexyl-2(S)-[(methanesulfonyliminophenyl-methyl)amino]propionamide;
- N-[1-(benzoxazol-2-ylcarbonyl)propyl]-2(R)-(1-cyclopentylamino-2-methanesulfonyl-vinylamino)-3-cyclopropylmetanesulfonylpropionamide;
- 10 N-[1-(benzoxazol-2-ylcarbonyl)-propyl]-3-cyclohexyl-2(S)-[(morpholin-4-yl-carboximidoyl)amino]propionamide;
- N-[1(S)-(benzoxazol-2-ylhydroxymethyl)propyl]-3-cyclohexyl-2(S)-[(methanesulfonyl-iminomethyl)amino]propionamide;
- ({1-[1(S)-(benzoxazol-2-ylcarbonyl)-propylcarbamoyl]-2(R)-phenylmethane-sulfonylethylamino}phenylmethylenecarbamic acid ethyl ester;
- 15 N-[(R)-1-(cyanomethylcarbamoyl)-2-p-tolylmethanesulfonylethyl]benzamide;
- N-(2-benzylsulfonyl-1R-cyanomethylcarbamoylethyl)benzamide;
- N-[1R-cyanomethylcarbamoyl-2-(4-methoxybenzylsulfonyl)ethyl]benzamide;
- N-(3-phenylsulfonyl-1R-cyanomethylcarbamoylpropyl)benzamide;
- 20 morpholine-4-carboxylic acid [(S)-1-(cyanomethylcarbamoyl)-3-(2-trifluoromethoxy-benzenesulfonyl)propyl]amide;
- morpholine-4-carboxylic acid [(S)-3-benzenesulfonyl-1-(cyanomethylcarbamoyl)propyl]-amide;
- morpholine-4-carboxylic acid [(S)-1-(cyanomethylcarbamoyl)-3-(4-trifluoromethoxy-benzenesulfonyl)propyl]amide;
- 25 thiophene-2-carboxylic acid [(S)-1-(cyanomethylcarbamoyl)-3-(2-trifluoromethoxy-benzenesulfonyl)propyl]amide;
- [(S)-1-(cyanomethylcarbamoyl)-3-(2-trifluoromethoxyphenylsulfanyl)propyl]carbamic acid *tert*-butyl ester;
- 30 3-acetyl-N-(2-benzylsulfonyl-1R-cyanomethylcarbamoylethyl)benzamide;
- N-(2-benzylsulfonyl-1R-cyanomethylcarbamoylethyl)naphthalene-2-carboxamide;
- N-(2-benzylsulfonyl-1R-cyanomethylcarbamoylethyl)furan-3-carboxamide;
- N-(2-benzylsulfonyl-1R-cyanomethylcarbamoylethyl)benzo[1,3]dioxole-5-carboxamide;

N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-3-pyridin-3-ylacrylamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)benzofuran-2-carboxamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)furan-2-carboxamide;
tert-butyl 2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethylcarbamate;
5 N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-3-phenoxybenzamide;
tert-butyl [3-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethylcarbamoyl)benzyl]-carbamate;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-4-hydroxybenzamide;
10 N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-3-hydroxybenzamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)thiophene-2-carboxamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)thiophene-3-carboxamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)quinoline-3-carboxamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)biphenyl-4-ylcarboxamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)quinoline-2-carboxamide;
15 4-benzoyl-N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)benzamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)nicotinamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)isonicotinamide;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethylmorpholine-4-carboxamide
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-3-methoxybenzamide;
20 ethyl 4-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethylcarbamoyl)piperazine-1-carboxylate;
tert-butyl 4-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethylcarbamoyl)piperazine-1-carboxylate;
N-(2-benzylsulfonyl-1*R*-cyanomethylcarbamoylethyl)-4-fur-2-ylcarbonylpiperazine-
25 1-carboxamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl)ethyl]morpholine-4-carboxamide;
N-[2-(4-chlorobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(3,5-dimethylbenzylsulfanyl)ethyl]benzamide;
30 N-[1*R*-cyanomethylcarbamoyl-2-(4-trifluoromethylbenzylsulfanyl)ethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(4-trifluoromethoxybenzylsulfanyl)ethyl]benzamide;

- N-[1*R*-cyanomethylcarbamoyl-2-(4-trifluoromethylsulfanylbenzylsulfonyl)ethyl]benzamide;
- 5 *N*-[1*R*-cyanomethylcarbamoyl-2-(3-nitrobenzylsulfonyl)ethyl]benzamide;
- N*-(1*R*-cyanomethylcarbamoyl-2-pyridin-2-ylmethylsulfonylethyl)benzamide;
- N*-(1*R*-cyanomethylcarbamoyl-2-pyridin-4-ylmethylsulfonylethyl)benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(3,4-dichlorobenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(3-methylbenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(4-nitrobenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfonyl)ethyl]benzamide;
- 10 *N*-[1*R*-cyanomethylcarbamoyl-2-(3-trifluoromethylbenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(3-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N*-(1*R*-cyanomethylcarbamoyl-2-pyridin-3-ylmethylsulfonylethyl)benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 15 *N*-(1*R*-cyanomethylcarbamoyl)-2-pentafluorobenzylsulfonylethyl)benzamide;
- N*-(1*R*-cyanomethylcarbamoyl-2-naphth-2-ylbenzylsulfonylethyl)benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-fluorobenzylsulfonyl)ethyl]benzamide;
- N*-[2-(2-chlorobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-(1*R*-cyanomethylcarbamoyl-2-prop-2-en-1-ylsulfonylethylbenzamide;
- 20 *N*-[2-(2-bromobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-iodobenzylsulfonyl)ethyl]benzamide;
- N*-[2-(4-*tert*-butylbenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-trifluoromethylbenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl]-2-(2-cyanobenzylsulfonyl)ethyl]benzamide;
- 25 *N*-[2-(4-bromobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-[2-(3-chlorobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(3-fluorobenzylsulfonyl)ethyl]benzamide;
- N*-[2-(3-chloro-2-fluorobenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N*-[1-cyanomethylcarbamoyl-2-(2-fluoro-3-methylbenzylsulfonyl)ethyl]benzamide;
- 30 *N*-[1-cyanomethylcarbamoyl)-2-(2,5-difluorobenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl)-2-(4-iodobenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl)-2-(3-iodobenzylsulfonyl)ethyl]benzamide;

N-[1R-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2,5-dichlorobenzylsulfonyl)ethyl]benzamide;
N-[2-(3-bromobenzylsulfonyl)-1-cyanomethylcarbamoylethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(3-cyanobenzyl)ethyl]benzamide;
5 *N-[1R-cyanomethylcarbamoyl-2-(4-cyanobenzylsulfonyl)ethyl]benzamide;*
N-[1R-cyanomethylcarbamoyl-2-(2-fluoro-6-nitrobenzylsulfonyl)ethyl]benzamide;
N-[2-(2-bromo-5-fluorobenzylsulfonyl)-1R-cyanomethylcarbamoylethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2,3-difluorobenzylsulfonyl)ethyl]benzamide;
10 *N-[2-biphenyl-2-ylmethylsulfonyl)-1R-cyanomethylcarbamoylethyl]benzamide;*
N-[1R-cyanomethylcarbamoyl]-2-(2,4-difluorobenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(4-fluorobenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(3,4-difluorobenzylsulfonyl)ethyl]benzamide;
15 *N-[1R-cyanomethylcarbamoyl-2-(2,3,4-trifluorobenzylsulfonyl)ethyl]benzamide;*
N-[1R-cyanomethylcarbamoyl-2-(2,4,6-trifluorobenzylsulfonyl)ethyl]benzamide;
N-[2-(2-chloro-5-trifluoromethylbenzylsulfonyl)-1R-cyanomethylcarbamoylethyl]-
benzamide;
20 *N-[2-(2,4-bistrifluoromethylbenzylsulfonyl)-1R-cyanomethylcarbamoylethyl]-benzamide;*
N-[1R-cyanomethylcarbamoyl-2-(2-fluoro-6-trifluoromethylbenzylsulfonyl)ethyl]-
benzamide;
25 *N-[1R-cyanomethylcarbamoyl-2-(2-fluoro-3-trifluoromethylbenzylsulfonyl)ethyl]-*
benzamide;
N-[1R-cyanomethylcarbamoyl-2-(3-trifluoromethylsulfanylbenzylsulfonyl)ethyl]-
benzamide;
30 *N-[1R-cyanomethylcarbamoyl-2-(2-fluoro-4-trifluoromethylbenzylsulfonyl)ethyl]-*
benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2,3,5-trifluorobenzylsulfonyl)ethyl]benzamide;
N-[1R-cyanomethylcarbamoyl-2-(2-trifluoromethylsulfanylbenzylsulfonyl)ethyl]-
benzamide;
N-[1R-cyanomethylcarbamoyl-2-(4-fluoro-2-trifluoromethylbenzylsulfonyl)ethyl]-
benzamide;

- N-[1*R*-cyanomethylcarbamoyl-2-(2-fluoro-5-trifluoromethylbenzylsulfonyl)ethyl]-benzamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(2-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N-{(R)-1-(cyanomethyl-carbamoyl)-2-[4-(1,1-difluoromethoxy)phenylmethanesulfonyl]}-5 ethyl}-benzamide;
- N-[2-(3,5-bistrifluoromethylbenzylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]-benzamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(2-methoxybenzylsulfonyl)ethyl]benzamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(2,6-dichlorobenzylsulfonyl)ethyl]benzamide;
- N-(1*R*-cyanomethylcarbamoyl-3-pyridin-4-ylsulfonylpropyl)benzamide;
- N-(1*R*-cyanomethylcarbamoyl)-3-pyridin-2-ylsulfonylpropyl)benzamide;
- N-(1*R*-cyanomethylcarbamoyl-2-(3-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(4-fluoro-3-trifluoromethylbenzylsulfonyl)ethyl]-10 benzamide;
- 4-(2*R*-benzoylamino-2-cyanomethylcarbamoylethylsulfonylmethyl)benzoic acid;
- N-[1*R*-(1-cyanocyclopropylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- N-[1*R*-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-15 morpholine-4-carboxamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- morpholine-4-carboxylic acid {(R)-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;
- N-[1*R*-cyanomethylcarbamoyl-2-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)ethyl]-20 benzamide;
- N-[2-(5-chlorothien-2-ylmethylsulfonyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
- N-[1*R*-cyanomethylcarbamoyl-2-(2-fluoro-3-methylbenzylsulfonyl)ethyl]benzamide;
- N-[1-(cyanomethylcarbamoyl)-2-(1-oxy-pyridin-2-ylmethanesulfonyl)ethyl]benzamide;
- N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]}-25 ethyl}-1-oxy-nicotinamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]}-30 ethyl}nicotinamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]}-ethyl}-isonicotinamide;

- 5 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-1-oxy-isonicotinamide;
- 10 pyridine-2-carboxylic acid {(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;
- 15 pyrazine-2-carboxylic acid {(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;
- 20 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-2-hydroxynicotinamide;
- 25 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-6-hydroxynicotinamide;
- 30 2-amino-*N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl} nicotinamide;
- 35 6-amino-*N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} nicotinamide;
- 40 3-hydroxypyridine-2-carboxylic acid {(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}-amide;
- 45 morpholine-4-carboxylic acid {(*R*)-1-(4-cyanotetrahydropyran-4-ylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl} amide;
- 50 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(3-pyridin-3-yl-ureido)propionamide;
- 55 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(3-pyridin-4-yl-ureido)propionamide;
- 60 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-(3-isopropyl-ureido)propionamide;
- 65 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(3,3-dimethyl-ureido)propionamide;
- 70 (*R*)-2-acetylamino-*N*-cyanomethyl-3-phenylmethanesulfonylpropionamide;
- 75 *N*-[*(R*)-1-(cyanomethylcarbamoyl)-2-phenylmethanesulfonylethyl]-2-methoxybenzamide;
- 80 *N*-[*(S*)-1-(cyanomethylcarbamoyl)-3-phenylmethanesulfonylpropyl]benzamide;
- 85 morpholine-4-carboxylic acid {(*R*)-1-[(1,1-dicyanomethyl)carbamoyl]-2-phenylmethanesulfonylethyl} amide;
- 90 2-(2-benzenesulfonylethyl)-*N*-benzyl-*N*'-cyanomethylmalonamide;

- {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-carbamic acid methyl ester;
- {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-carbamic acid allyl ester;
- 5 {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl} carbamic acid isopropyl ester;
- {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl} carbamic acid isobutyl ester;
- (R)-N-cyanomethyl-2-(1-oxo-1,3-dihydroisoindol-2-yl)-3-phenylmethanesulfonyl-
10 propionamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3,4-difluorobenzamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3,4-dimethoxybenzamide;
- 15 N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3-methylbenzamide;
- thiophene-3-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-amide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy-phenylmethanesulfonyl]-ethyl}-4-fluorobenzamide;
- 20 4-methylpentanoic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl} amide;
- thiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;
- 25 4-bromo-N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}benzamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-4-methoxybenzamide;
- N-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-4-trifluoromethoxybenzamide;
- 30 naphthalene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;

- (E)-*N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethane-sulfonyl]ethyl}-3-phenylacrylamide;
- 5 5-methylthiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]ethyl} amide;
- 5 biphenyl-4-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-amide;
- 10 1*H*-indole-5-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]ethyl} amide;
- 10 benzo[1,3]dioxole-5-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]ethyl} amide;
- 15 benzo[b]thiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]ethyl} amide;
- 15 *N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-3-phenoxybenzamide;
- 20 quinoline-3-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl} amide;
- 20 *N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3-(1-phenyl-methanoyl)-benzamide;
- 20 4-chloro-*N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenyl-methanesulfonyl]ethyl}benzamide;
- 25 *N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3-fluoro-4-methoxy-benzamide;
- 25 3-bromohiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]ethyl}-amide;
- 30 3-chlorobenzo[b]thiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl} amide;
- 30 3-chlorothiophene-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]ethyl} amide;
- 30 *N*-{(R)-(cyanomethylcarbamoyl)-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}-trifluoromethylbenzamide;
- 30 quinoline-2-carboxylic acid {(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;

- (*R*)-2-benzenesulfonylamino-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]propionamide;
- (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(naphthalene-2-sulfonylamino)propionamide;
- 5 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-(thiophene-2-sulfonylamino)propionamide;
- cyclopentanecarboxylic acid {(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl} amide;
- 10 morpholine-4-carboxylic acid {(*R*)-1-[(1-cyano-1-thiophen-2-ylmethyl)carbamoyl]-2-phenylmethanesulfonylethyl} amide;; and
- morpholine-4-carboxylic acid {(*R*)-1-[(1-cyano-1-furan-2-ylmethyl)carbamoyl]-2-phenylmethanesulfonylethyl} amide; or
- a pharmaceutically acceptable salts thereof.

Syntheses of the above specific compounds are described in PCT Applications Publication 15 Nos. WO 00/55144, WO 00/07145, WO 00/55125, WO 01/19796, WO 02/051983, WO 02/098850, WO 02/098406, WO 03/024924, and PCT Application No. US03/19990.

Preferably, the Cathepsin S inhibitor is administered prior to the administration of the biological agent.

20 Preferably, the Cathepsin S inhibitor is administered concomitantly with the biological agent.

Preferably, the Cathepsin S inhibitor is administered after the administration of the biological agent.

DETAILED DESCRIPTION OF THE INVENTION

25 Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means cycloalkyl and heterocycloalkyl rings as defined herein.

30 "Alkyl" represented by itself means a straight or branched, saturated aliphatic radical containing one to six carbon atoms, unless otherwise indicated (e.g., alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated aliphatic divalent

radical having the number of atoms indicated (e.g., aralkyl includes benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like). It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy" "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom.

"Alkylene", unless indicated otherwise, means a straight or branched, saturated aliphatic, divalent radical having the number of one to six carbon atoms, e.g., methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-), and the like.

"Alkylcarbamoyloxy" refers to a radical -OCONHR where R is an alkyl group e.g., methylcarbamoyloxy, ethylcarbamoyloxy, and the like.

"Alkylsulfonylamino" refers to a radical -NHSO₂R where R is an alkyl group e.g., methylsulfonylamino, ethylsulfonylamino, and the like.

"Amino" means the radical -NH₂.

"Aminosulfonyl" refers to a radical -SO₂NH₂.

"Alkylaminosulfonyl" or "dialkylaminosulfonyl" refers to a radical -SO₂NHR and -SO₂NRR' respectively, where R and R' are independently alkyl group e.g., methylaminosulfonyl, and the like.

"Alkylaminocarbonyl" or "dialkylaminocarbonyl" refers to a radical -CONHR and -CONRR' respectively, where R and R' are independently alkyl group e.g., methylaminocarbonyl, and the like.

"Alkylamino" or "dialkylamino" refers to a radical -NHR and -NRR' respectively, where R and R' are independently alkyl group e.g., methylamino, dimethylamino, and the like.

"Alkoxy" refers to a radical -OR where R is an alkyl group e.g., methoxy, ethoxy, and the like.

"Alkoxycarbonyl" refers to a radical -C(O)OR where R is an alkyl group e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

"Alkoxycarbonylalkyl" means the radical -(alkylene)-C(O)OR where R is alkyl as defined above e.g., methoxycarbonylalky, 2-, or 3-ethoxycarbonylmethyl, and the like.

"Alkoxycarbonylamino" refers to a radical -NHC(O)OR where R is an alkyl group e.g., methoxycarbonylamino, ethoxycarbonylamino, and the like.

- "Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one alkoxy group, preferably one or two alkoxy groups, as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.
- 5 "Alkoxyalkyloxyalkyl" refers to a radical -(alkylene)-O-(alkylene)-OR where R is an alkyl group e.g., as defined above, e.g., 2-methoxyethyloxymethyl, 3-methoxypropyloxyethyl, and the like.
- 10 "Aminoalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, preferably one or two, -NRR' where R is hydrogen, alkyl, or -COR^a where R^a is alkyl, and R' is hydrogen or alkyl, e.g., aminomethyl, methylaminoethyl, dimethylaminoethyl, 1,3-diaminopropyl, acetylaminopropyl, and the like.
- 15 "Alkylthio" refers to a radical -SR where R is an alkyl group e.g., methylthio, ethylthio, and the like.
- 20 "Alkylsulfinyl" refers to a radical -S(O)R where R is an alkyl group e.g., methylsulfinyl, ethylsulfinyl, and the like.
- "Alkylsulfonyl" refers to a radical -SO₂R where R is an alkyl group e.g., methylsulfonyl, ethylsulfonyl, and the like.
- 25 "Acyl" means a radical -COR where R is hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl as defined herein, e.g., formyl, acetyl, trifluoroacetyl, benzoyl, piperazin-1-ylcarbonyl, and the like.
- "Alkanoyl" means the radical -COR where R is alkyl as defined above e.g., acetyl, propionyl, and the like.
- 30 "Alkanoylamino" means the radical -NHCOR where R is alkyl as defined above e.g., acetylamino, propionylamino, and the like.
- "Acyloxy" means a radical -OCOR where R is alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl as defined herein, e.g., acyloxy, trifluoroacetyloxy, benzyloxy, piperazin-1-ylcarbonyloxy, and the like.
- "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).
- "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are *sp*² hybridized and the total number of pi electrons is equal

to $4n+2$.

"Aryl" means a monocyclic or fused bicyclic ring assembly containing 6 to 10 ring carbon atoms unless otherwise indicated, wherein each ring is aromatic e.g., phenyl or anthryl.

5 "Aralkyl" means a radical -(alkylene)-R where R is aryl as defined above e.g., benzyl, phenethyl, and the like.

"Aryloxy" means a radical -OR where R is aryl as defined above.

"Aryloxyalkyl" means the radical -(alkylene)-OR where R is aryl as defined above e.g., phenoxyethyl, 2-, or 3-phenoxyethyl, and the like

10 "Aryloxycarbonyl" means the radical -C(O)OR where R is aryl as defined above e.g., phenyloxycarbonyl, and the like.

"Aralkyloxycarbonyl" means the radical -C(O)OR where R is aralkyl as defined above e.g., benzyloxycarbonyl, and the like.

"Arylcarbamoyloxy" means the radical -OC(O)NHR where R is aryl as defined above e.g., phenylcarbamoyloxy, and the like.

15 "Aroyl" means the radical -COR where R is aryl as defined above e.g., benzoyl.

"Aroylamino" means the radical -NHCOR where R is aryl as defined above e.g., benzoylamino, and the like.

"Arylthio" refers to a radical -SR where R is an aryl group e.g., phenylthio, and the like.

20 "Arylsulfinyl" refers to a radical -SOR where R is an aryl group e.g., phenylsulfinyl, and the like.

"Arylsulfonyl" refers to a radical -SO₂R where R is an aryl group e.g., phenylsulfonyl, and the like.

"Aryloxycarbonylamino" refers to a radical -NHC(O)OR where R is an aryl group e.g., phenoxy carbonylamino, and the like.

25 "Arylsulfonylamino" refers to a radical -NHSO₂R where R is an aryl group as defined above, unless otherwise stated e.g., phenylsulfonylamino, and the like.

"Arylaminosulfonyl" means the radical -SO₂NHR where R is aryl as defined above e.g., phenylaminosulfonyl, and the like.

30 "Aralkylaminosulfonyl" means the radical -SO₂NHR where R is aralkyl as defined above e.g., benzylaminosulfonyl, and the like.

"Arylaminocarbonyl" means the radical -CONHR where R is aryl as defined above e.g., phenylaminosulfonylcarbonyl, and the like.

"Aralkylaminocarbonyl" means the radical $-CONHR$ where R is aralkyl as defined above e.g., benzylaminocarbonyl, and the like.

"Biologic" means a therapeutic agent originally derived from living organisms for the treatment or management of a disease. Examples include, but are not limited to, proteins 5 (recombinant and plasma derived), monoclonal or polyclonal, humanized or murine antibodies, toxins, hormones, and the like. Biologics are currently available for the treatment of a variety of diseases such as cancer, rheumatoid arthritis, and haemophilia.

"Carboxamide" means the radical $-C(O)NH_2$.

"Carbamoyl" or "aminocarbonyl" means the radical $-C(O)NRR'$ where R and R' are 10 independently selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl provided one of R and R' is not hydrogen.

"Carboxy" means the radical $-C(O)OH$.

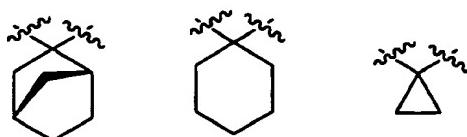
"Carboxyalkyl" means the radical $-(alkylene)-C(O)OH$ e.g., carboxymethyl, carboxyethyl, and the like.

15 "Cycloalkyl" means a monovalent saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing three to eight ring carbon atoms e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, and the like.

"Cycloalkylalkyl" means the radical $-(alkylene)-R$ where R is cycloalkyl as defined above 20 e.g., cyclopropylmethyl, cyclobutylethyl, cyclobutylmethyl, and the like

"Cycloalkyloxy" means the radical $-OR$ where R is cycloalkyl as defined above e.g., cyclobutyloxy, pentyloxy, hexyloxy, and the like.

25 "Cycloalkylene" means a divalent saturated or partially unsaturated monocyclic ring or bridged polycyclic ring assembly containing three to eight ring carbon atoms. For example, the instance wherein " R^1 and R^{1a} together with the carbon atom to which both R^1 and R^{1a} are attached form cycloalkylene" includes, but is not limited to, the following:



30 "Disubstituted amino" means a radical $-NRR'$ where R is alkyl, aryl, aralkyl, heteroaryl,

heteraralkyl, or heterocycloalkyl, and R' is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, or acyl. Representative examples include, but are not limited to, dimethylamino, methylphenylamino, benzylmethylamino, acetyl methylamino, and the like.

5 "Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Deleterious immune response" means an immune response that prevents effective treatment of a patient or causes disease in a patient. As an example, dosing a patient with a murine antibody either as a therapy or a diagnostic agent causes the production of human antimouse antibodies that prevent or interfere with subsequent treatments. The incidence of antibody formation versus pure murine monoclonals can exceed 70%. (see Khazaeli, M. B. et al. "Human immune response to monoclonal antibodies", *J. Immunother.* 1994, 15, 42-52; Dillman R. O. et al. "Human anti-mouse antibody response in cancer patients following single low-dose injections of radiolabeled murine monoclonal antibodies". *Cancer Biother.* 1994, 9, 17-28; and Reinsberg, J. "Interference by human antibodies with tumor marker assays". *Hybridoma.* 1995, 14, 205-208). Additional examples of known agent that suffer from deleterious immune responses are blood-clotting factors such as factor VIII. When administered to hemophilia A patients, factor VIII restores the ability of the blood to clot. Although factor VIII is a human protein, it still elicits an immune response in hemophiliacs as endogenous factor VIII is not present in their blood and thus it appears as a foreign antigen to the immune system.

Approximately 29-33% of new patients will produce antibodies that bind and neutralize the therapeutically administered factor VIII (see Lusher J. M. First and second generation recombinant factor VIII concentrates in previous untreated patients: recovery, safety efficacy , and inhibitor development. *Semin Thromb Hemost.* 2002, 28(3), 273-276). These neutralizing antibodies require the administration of larger amounts of factor VIII in order to maintain normal blood clotting parameters; an expensive regimen of treatment in order to induce immune tolerance (see Briet E et al. The incidence of inhibitors in hemophilia A and the induction of immune tolerance. *Adv. Exp. Med. Bio.* 2001, 489, 89-97). Another immunogenic example is adenoviral vectors.

30 Retroviral therapy remains experimental and is of limited utility. One reason is that the application of a therapeutic virus generates an immune response capable of blocking any subsequent administration of the same or similar virus (see Yiping Yang et al. Cellular and

- Humoral Immune Reponses to Viral Antigen Create Barrier to Lung-Directed Gene Therapy with Recombinant Adenoviruses. *J. of Virology*. 1995, 69, 2004-2015). This ensures that retroviral therapies must be based on the transient expression of a protein or the direct incorporation of viral sequence into the host genome. Directed research has identified multiple viral neutralizing epitopes recognized by host antibodies (see Hanne, Gahery-Segard et al. Immune Response to Recombinant Capsid Proteins of Adenovirus in Humans: Antifiber and Anti-Penton Base Antibodies has a Synergistic Effect on Neutralizing Activity. *J. of Virology* 1998. 72, 2388-2397) suggesting that viral modifications will not be sufficient to overcome this obstacle. This invention will enable a process whereby an adenoviral therapy will have utility for repeated application.
- 5 Another example of an immunogenic agent that elicits neutralizing antibodies is the well-known cosmetic agent Botox. Botulin toxin protein, is purified from the fermentation of *Clostridium botulinum*. As a therapeutic agent, it is used for muscle disorders such as cervical dystonia in addition to cosmetic application. After repeated exposure patients generate neutralizing antibodies to the toxin that results in reduced efficacy (see Birklein F. et al. Sudomotor testing predicts the presence of neutralizing botulinum A toxin antibodies. *Ann Neurol.* 2002, 52, 68-73 and Rollnik, J. D. et al. Neutralizing botulinum toxic type a antibodies: clinical observations in paitent with cervical dystonia. *Neurol. Clin. Neurophysiol.* 2001, 2001(3), 2-4). A “deleterious immune response” also encompasses diseases caused by the biologic agents. A specific example of this is the immune response to therapy with recombinant human erythropotetin (EPO). Erythropotetin is used to stimulate the growth of red cells and restore red blood cell counts in patients who have undergone chemotherapy or dialysis. A small percentage of patients develop antibodies to EPO and subsequently are unresponsive to both therapeutically administered EPO and their own endogenous EPO (see Casadevall, N. et al., Pure red-cell aplasia and anti-erythropoietin antibodies in patients treated with recombinant erythropoietin. *NEJM*. 2002, 346:469-475). They contract a disorder, pure red cell aplasia, in which red blood cell production is severely diminished (see Gershon S. K. et. al. Pure red-cell aplasia and recombinant erythropoietin. *NEJM*. 2002, 346:1584-1586). This complication of EPO therapy is lethal if untreated. Another specific example is the murine antibody, OKT3 (a.k.a., Orthoclone) a monoclonal antibody directed towards CD-3 domain of activated T-cells. In clinical trials 20-40% of patients administered OKT3 produce antibodies versus the therapy. These antibodies besides neutralizing the therapy also stimulate a strong host immune reaction. The immune reaction is severe enough that patients with high titers of human anti-mouse antibodies are specifically restricted from taking the drug (see Orthoclone
- 10
- 15
- 20
- 25
- 30

package label). A final example is a human antibody therapeutic. Humira® is a monoclonal antibody directed against TNF and is used to treat rheumatoid arthritis patients. When taken alone ~12% of patients develop neutralizing antibodies. In addition, a small percentage of patients given the drug also contract a systemic lupus erthematosus-like condition that is an IgG-mediated immune response induced by the therapeutic agent (see Humira package label).

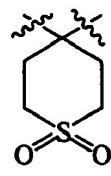
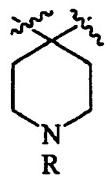
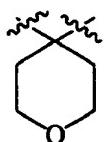
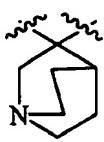
5 "Derived" means a similar agent can be traced to.

"Halo" means fluoro, chloro, bromo or iodo.

10 "Haloalkyl" means alkyl substituted by one or more, preferably one to five, "halo" atoms, as such terms are defined in this Application. Haloalkyl includes monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like e.g. chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Haloalkoxy" refers to a radical -OR where R is haloalkyl group as defined above e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

15 "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more, preferably one or two, of the ring member carbon atoms is replaced by a heteroatom selected from -N-, -O-, -S- or -S(O)₂- and optionally one or two ring member carbon atoms are replaced with -C(O)-. For example, the instance wherein R⁵ and R⁶ together with the carbon atom to which both R⁵ and R⁶ are attached form heterocycloalkylene" includes, but is not limited to, the
20 following:



in which R is a substituent defined in the Summary of the Invention

25 "Heteroaryl" means an aromatic monocyclic or multicyclic ring of 5 to 10 ring atoms in which one or more, preferably one, two, or three, of the ring atoms are selected from nitrogen, oxygen or sulfur, the remaining ring atoms being carbon. Representative heteroaryl rings include, but are not limited to, pyrrolyl, furanyl, thieryl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzofuranyl,

benzothienyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolyl, and the like.

"Heteroaralkyl" means a radical -(alkylene)-R where R is heteroaryl as defined above e.g., pyridinylmethyl, 1- or 2-furanylethyl, imidazolylmethyl, and the like.

5 "Heteroaryloxyalkyl" means the radical -(alkylene)-OR where R is heteroaryl as defined above e.g., furanyloxymethyl, 2-, or 3-indolyloxyethyl, and the like.

"Heteroarylsulfonyl" refers to a radical -SO₂R where R is an heteroaryl group e.g., pyridinylsulfonyl, and the like.

10 "Heteroarylsulfonylamino" refers to a radical -NHSO₂R where R is an heteroaryl group e.g., pyridinylsulfonylamino, and the like.

"Heteroaralkylsulfonylamino" refers to a radical -NHSO₂R where R is an heteroaralkyl group e.g., pyridinylmethysulfonylamino, and the like.

15 "Heteroaryloxycarbonyl" means the radical -C(O)OR where R is heteroaryl as defined above e.g., furanyloxycarbonyl, 2-, or 3-indolyloxycarbonyl, and the like.

"Heteroaralkyloxycarbonyl" means the radical -C(O)OR where R is heteroaralkyl as defined above e.g., furanylmethyloxycarbonyl, 2-, or 3-indolethoxy carbonyl, and the like.

20 "Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more, preferably one, two, or three of the ring carbon atoms indicated are replaced by a heteroatom selected from -N-, -O-, -S-, -SO-, or -S(O)₂- and additionally one or two carbon atoms are optionally replaced by -C(O). Representative examples include, but are not limited to, imidazolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyranyl, 1,1-dioxotetrathiopyranyl, indolinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like.

25 "Heterocycloalkylalkyl" means -(alkylene)-heterocycloalkyl as defined in this Application. Representative examples include, but are not limited to, imidazolidin-1-ylmethyl, morpholin-4-ylmethyl, thiomorpholin-4-ylmethyl, thiomorpholin-4-ylmethyl-1-oxide, indolinylethyl, piperazinylmethyl or ethyl, piperidylmethyl or ethyl, pyrrolidinylmethyl or ethyl, and the like.

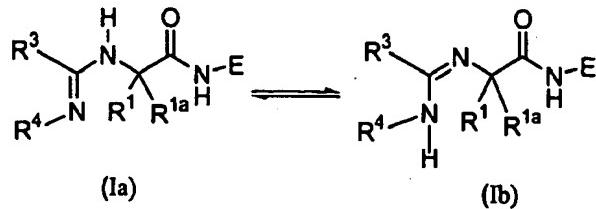
30 "Hydroxy" means the radical -OH.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same

carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl,
5 preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Isomers" mean compounds of the present invention having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed
10 "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with
15 more than one chiral center may exist as either an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described
20 by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula (Ia) or (Ib) are meant to be
25 encompassed all possible stereoisomers.

Additionally, compounds of Formula (Ia) and (Ib) may exist as tautomers. Such tautomeric forms (individual tautomers or mixtures thereof) are within the scope of this invention. For example, a compound of Formula (Ia) where R² is hydrogen can tautomerize to give a compound of Formula (Ib) where R^{4a} is hydrogen and vice versa as shown below.



It will be recognized by a person skilled in the art that the amount of tautomers will vary based on certain conditions such as steric interactions, electronic effects of substituents, solvent polarity, hydrogen bonding capability, temperature, pH, and the like.

"Cathepsin S inhibitor" is any molecular species which inhibits the transcription of a cathepsin S gene, the processing or translation of a cathepsin S mRNA, or the processing, trafficking or activity of a cathepsin S protein, when administered in vivo or in vitro to a mammalian cell which is otherwise competent to express active cathepsin S. Thus, for example,

10 the term "inhibitor of cathepsin S" embraces a repressor which inhibits induction and/or transcription of the cathepsin S gene, or an antisense sequence which selectively binds to cathepsin S DNA or mRNA sequences and which inhibits the transcription or translation of the cathepsin S sequences. Similarly, the term "inhibitor of cathepsin S" includes competitive, uncompetitive and non-competitive inhibitors of the activity of the cathepsin S protein, such as

15 small molecules which structurally mimic the natural substrates of cathepsin S but which are resistant to the proteolytic activity of the enzyme. Although an inhibitor of cathepsin S may have some degree of inhibitory activity for other genes or proteins which are structurally or functionally related, the term "inhibitor of cathepsin S" is not intended to embrace non-selective suppressors of all gene expression or protein synthesis, or general toxins (e.g., transcription blockers such as

20 actinomycin D, and alpha.-amanitin, protein synthesis inhibitors such as puromycin, cycloheximide, and diphtheria toxin).

"Keto or oxo" means the radical (=O).

"Monosubstituted amino" means a radical $-NHR$ where R is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, or acyl as defined herein.

25 Representative examples include, but are not limited to, methylamino, phenylamino, benzylamino, cycloalkylmethylamino, acetylamino, trifluoroacetyl, and the like.

"Nitro" means the radical -NO_2 .

"Optional" or "optionally" or "may be" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or

circumstance occurs and instances in which it does not. For example, the phrase "wherein the aromatic ring R^a is optionally substituted with one or two substituents independently selected from alkyl." means that the aromatic ring may or may not be substituted with alkyl in order to fall within the scope of the invention.

5 The present invention also includes *N*-oxide derivatives of the compounds of this invention. *N*-oxide derivatives means derivatives of compounds of the present invention in which nitrogens are in an oxidized state (i.e., N→O) e.g., pyridine *N*-oxide, and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease
10 as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention
15 which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid,
20 malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methylsulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid,
25 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable
30 inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

The present invention also includes prodrugs of a compound of the present invention.

- Prodrug means a compound that is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of the present invention. For example an ester of a compound of the present invention containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of the present invention containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of the present invention containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methylsulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of the present invention containing a carboxy group, are for example those described by Leinweber, F.J. Drug Metab. Res., 1987, 18, pg. 379. An especially useful class of esters of compounds of the present invention containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of the present invention in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of the present invention are useful in the preparation of compounds of the present invention or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" means any administration of a Cathepsin S inhibitor of the present invention and includes:

- (1) preventing the immune response from occurring in an animal which may be predisposed to the immune response but does not yet experience or display the pathology or symptomatology of the immune response,
- (2) inhibiting the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., arresting further development of the pathology and/or symptomatology), or
- (3) ameliorating the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., reducing in degree or severity, or extent or duration, the overt manifestations of the immune response or reversing the pathology and/or symptomatology e.g., reduced binding and presentation of antigenic peptides by MHC class II molecules, reduced activation of T-cells and B-cells, reduced humoral and cell-mediated responses and, as appropriate to the particular immune response, reduced inflammation, congestion, pain, necrosis, reduced loss in the efficacy of a biologic agent, and the like).

15 Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of this invention are preferred. For example:

(I). A preferred group of compounds is of Formula (Ia) and (Ib):

Within this group (I):

20 A. One preferred group of compounds is that wherein E is $-C(R^5)(R^6)X^1$ in which:

R^5 is hydrogen or alkyl; and

R^6 is hydrogen, alkyl, -(alkylene)-OR¹² (where R¹² is hydrogen, alkyl or haloalkyl), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in aryl, aralkyl, heteroaryl,

25 heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl is optionally substituted with one, two, or three R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino, or acyl.

Preferably, R^5 is hydrogen;

R^6 is alkyl, preferably ethyl; and

30 X^1 is $-CHO$, $-C(O)R^{10}$, $-C(O)CF_3$, $-C(O)CF_2CF_2R^9$, $-CH=CHS(O)_2R^{10}$, $-C(O)CF_2C(O)NR^{10}R^{11}$, $-C(O)C(O)NR^{10}R^{11}$, $-C(O)CH_2OR^{10}$, $-C(O)CH_2N(R^{11})SO_2R^{10}$, $-C(O)C(O)N(R^{11})(CH_2)_2OR^{11}$, $-C(O)C(O)N(R^{11})(CH_2)_2NHR^{11}$ or $-C(O)C(O)R^{10}$ wherein R¹⁰ is

alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl wherein the aromatic ring is optionally substituted with R^d selected from heteroaryl, aryl, or alkyl, R¹¹ is hydrogen or alkyl and R⁹ is halo.

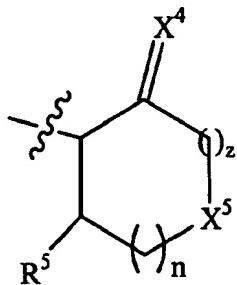
Preferably, E is $-\text{CHR}^6\text{C(O)R}^{10}$ where R⁶ is alkyl, preferably ethyl, propyl, or butyl, more preferably ethyl, and R¹⁰ is heteroaryl optionally substituted with one or two R^d independently selected from alkyl, haloalkyl, alkoxy, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, aryl, heteroaryl, amino, monosubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in R^d is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino, more preferably R¹⁰ is benzoxazol-2-yl, 4-azabenzoxazol-2-yl, 2-pyridin-3-yl-[1,3,4]-oxadiazol-5-yl, 2-pyridin-4-yl-[1,3,4]-oxadiazol-5-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-isopropyl-[1,3,4]-oxadiazol-5-yl, 2-*tert*-butyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl, 2-furan-2-yl-[1,3,4]-oxadiazol-5-yl, 2-thien-2-yl-[1,3,4]-oxadiazol-5-yl, 2-(4-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-dimethylaminophenyl)-[1,3,4]-oxadiazol-5-yl, pyradizin-3-yl, pyrimidin-2-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 3-cyclopropyl-[1,2,4]-oxadiazol-5-yl, 3-thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-4-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-2-yl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, 5-phenyl-[1,2,4]-oxadiazol-3-yl, 5-thien-3-yl-[1,2,4]-oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]-oxadiazol-3-yl, 5-pyridin-4-yl-[1,2,4]-oxadiazol-3-yl, or 5-phenyloxazol-2-yl, most preferably benzoxazol-2-yl.

B. Another preferred group of compounds is that wherein E is $-\text{C(R}^5)(\text{R}^6)\text{X}^1$ in which R⁵ and R⁶ taken together with the carbon atom to which both R⁵ and R⁶ are attached form cycloalkylene or heterocycloalkylene, preferably cyclopropylene, cyclopentylene, cyclohexylene, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-4-yl-1-oxide, tetrahydrothiopyran-4-yl-1,1-dioxide, or piperidin-4-yl wherein the nitrogen atom is optionally substituted with alkyl or hydroxy, preferably tetrahydrothiopyran-4-yl-1,1-dioxide, and X¹ is -CHO, $-\text{C(O)R}^{10}$, $-\text{C(O)CF}_3$, $-\text{C(O)CF}_2\text{CF}_2\text{R}^9$, $-\text{CH=CHS(O)}_2\text{R}^{10}$, $-\text{C(O)CF}_2\text{C(O)NR}^{10}\text{R}^{11}$, $-\text{C(O)C(O)NR}^{10}\text{R}^{11}$, $-\text{C(O)CH}_2\text{OR}^{10}$, $-\text{C(O)CH}_2\text{N}(\text{R}^{11})\text{SO}_2\text{R}^{10}$, $-\text{C(O)C(O)N}(\text{R}^{11})(\text{CH}_2)_2\text{OR}^{11}$,

- C(O)C(O)N(R¹¹)(CH₂)₂NR¹ or -C(O)C(O)R¹⁰. More preferably, -C(O)C(O)NR¹⁰R¹¹ where R¹¹ is hydrogen and R¹⁰ is benzyl.

C. Yet another preferred group of compounds is that wherein E is a group of formula (a):

5



in which:

n is 0, 1, or 2, z is 1, X⁴ is -NR²²-, -O- or -S- where R²² is hydrogen, alkyl, or alkoxy; X⁵ is -O-, -S(O)₂-, -S- or -NR²³- where R²³ is selected from hydrogen, alkyl, -S(O)₂R²⁴, -C(O)OR²⁶, 10 or acyl, - where R²⁴ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl and R²⁶ is hydrogen or alkyl. Preferably, z is 1, X⁴ is -O-, n is 0 or 1, and X⁵ is -O-.

D. Yet another preferred group of compounds is that wherein E is -CR^{5a}R^{6a}CN wherein R^{5a} and R^{6a} are hydrogen.

E. Within this group another preferred group of compounds is that wherein E is -CR^{5a}R^{6a}CN wherein R^{5a} and R^{6a} together with the carbon atom to which they are attached form cycloalkylene optionally substituted with one or two R^b independently selected from alkyl, halo, dialkylamino, 20 aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxycarbonyl. Preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene optionally substituted with groups described immediately above. More preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, 25 cycloheptylene, 2-methylcyclopropylene, 3-benzylcyclopentylene, 3-cyclohexylmethylcyclopentylene, 3-cyclopentylmethylcyclopentylene, 3-phenylcyclopentylene, 3-cyclohexylcyclopentylene, 3-cyclopentylcyclopentylene, 3-pyridin-2-ylmethylcyclopentylene, 3-

- pyridin-3-ylmethylcyclopentylene, 3-pyridin-4-ylmethylcyclopentylene, 2-methylcyclopropylene,
2,3-dimethylcyclopropylene, 3-benzylcyclobutylene, 3-methylcyclopentylene, 3,4-dimethylcyclopentylene, 3-ethylcyclopentylene, 3-(1,1-dimethylpropyl)-cyclopentylene, 3-n-butylcyclopentylene, 3-ethoxycarbonylcyclopentylene, 3,4-diethoxycarbonyl-cyclopentylene, or 3-benzyl-4-dimethylaminocyclopentylene. Most preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form cyclopropylene.

F. Yet another preferred group of compounds is that wherein E is -CR^{5a}R^{6a}CN wherein R^{5a} and R^{6a} together with the carbon atom to which they are attached form heterocycloalkylene optionally substituted with one to four alkyl or one or two R^c which are independently selected from alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)_{n2}R¹⁴, -alkylene-S(O)_{n2}-R¹⁵, -COOR¹⁶, -alkylene-COOR¹⁷, -CONR¹⁸R¹⁹, or -alkylene-CONR²⁰R²¹ (where n2 is 0-2 and R¹⁴-R¹⁷, R¹⁸ and R²⁰ are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and R¹⁹ and R²¹ are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino, or acyl. Preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiopyran-4-yl-1-oxide, tetrahydrothiopyran-4-yl-1,1-dioxide, hexahydropyridimidinyl, or hexahydropyridazinyl optionally substituted as described above. More preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form piperidin-4-yl substituted with one to three alkyl and one R^c selected from haloalkyl, aminoalkyl, alkoxycarbonyl, alkoxyalkyl, alkoxyalkyloxyalkyl, heterocycloalkyl, heterocycloalkylalkyl, -alkylene-CONR²⁰R²¹, or cycloalkyl wherein the alicyclic ring is optionally substituted with substituents listed above. Most preferably, R^{5a} and R^{6a} together with the carbon atom to which they are attached form piperidin-4-yl optionally substituted at the 1-position with methyl, ethyl, propyl, n-butyl, n-pentyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 3-morpholin-4-ylpropyl, 3-piperidin-1-yl-propyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(1-methylpiperidin-4-yl)propyl, 4-morpholin-4-ylbutyl, 2-(2-methoxyethoxy)ethyl, 4-

- methoxybutyl, 4-aminocarbonylbutyl, 3-aminocarbonylpropyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 1-ethoxycarbonylpiperidin-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, hydroxy, 2,2,2-trifluoroethyl, or *tert*-butyl, 1,2-dimethylpiperidin-4-yl, 1,2,6-trimethylpiperidin-4-yl, 1,2,2-trimethylpiperidin-4-yl, 1-methyl-2-oxopiperidin-4-yl, 1-methylpiperidin-3-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 1-cyclohexylpiperidin-4-yl, 1-cyclopropylmethylpyrrolidin-3-yl, 1-benzylpyrrolidin-3-yl, 1-benzyloxycarbonylpyrrolidin-3-yl, pyrrolidin-3-yl, 1-hydroxypyrrrolidin-3-yl, 1-methylpyrrolidin-3-yl, 1-ethypyrrrolidin-3-yl, 1-*n*-propyl or *n*-butylpyrrolidin-3-yl, 1-cyclohexylpyrrolidin-3-yl, 1-ethyl-2,2-dimethylpyrrolidin-4-yl, 1-propyl-2-methoxycarbonylpiperidin-4-yl, 2-oxopyrrolidin-3-yl, 1-ethyl-2-oxopyrrolidin-3-yl, morpholin-4-yl, 1-(1-methylpiperidin-4-ylcarbonyl)piperidin-4-yl, 1-ethoxycarbonylpiperidin-4-yl, 1-benzylazetidin-3-yl, tetrahydrothiopyran-4-yl-1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide.

(a) Within the above preferred and more preferred groups (A-F), a more preferred group of compounds is that wherein:

- 15 R^{1a} is alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaralkyl, cycloalkylalkyl, heterocycloalkylalkyl, or -alkylene-X²-R³² [wherein X² is -NR³³-, -O-, -S(O)_{n4}-, -CO-, -COO-, -OCO-, -NR³³CO-, -CONR³³-, -NR³³SO₂-, -SO₂NR³³-, -NR³³COO-, -OCONR³³-, -NR³³CONR³⁴, or -NR³³SO₂NR³⁴- (where R³³ and R³⁴ are independently hydrogen, alkyl, or acyl and n4 is 0-2) and R³² is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, 20 heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl] wherein said alkylene chain is optionally substituted with one to six halo and wherein the aromatic or alicyclic ring in R^{1a} is optionally substituted with one, two, or three R^c independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, monosubstituted amino, disubstituted 25 amino, or acyl; and

R¹ and R² are hydrogen.

Preferably, R^{1a} is 2-methylpropyl, 2,2-dimethylpropyl, 3,3-dimethylbutyl, 3-methylbutyl, 2,2,3-trimethylbutyl, 3,3-dimethylpentyl, 3-ethyl-3-methylpentyl, *n*-butyl, 2-methylbutyl, or 1-methylpropyl.

Preferably, R^{1a} is 4,4-dimethylcyclohexylmethyl, 4-ethyl-4-methylcyclohexylmethyl, 4,4-diethylcyclohexylmethyl, 3,3-dimethylcyclohexylmethyl, 3,5-dimethylcyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, 2-cyclohexylethyl, 2-cyclohexyl-2-methylpropyl, 2-(1-methylcyclohexyl)ethyl, 2-(1-methylcyclopropyl)ethyl, 2-(1-methylcyclopropyl)-2-methylpropyl,
5 2-cyclopentylethyl, 2-cyclopentyl-2-methylpropyl, 4-isopropyl-4-methylcyclohexylmethyl, 2-methylcyclohexylmethyl, 4-methoxycyclohexylmethyl, 1-methylcyclopentylmethyl, cyclohexyl, cyclohexylmethyl, 1,4-dimethylcyclopentylmethyl, cyclohexylethyl, cyclohexylmethyl, cyclopentylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, or 1-benzylcyclopropylmethyl, preferably 1-methylcyclopentylmethyl.

10

Preferably, R^{1a} is 2-bicyclo[2.2.1]hept-3-ylethyl, 8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylmethyl, bicyclo[3.2.1]oct-3-ylmethyl, bicyclo[3.1.1]hept-3-ylmethyl, 6,6-dimethylbicyclo[3.1.1]hept-3-ylmethyl, 6,6-dimethylbicyclo[3.1.1]hept-4-ylmethyl, 2-bicyclo[2.2.1]hept-1-ylethyl, or bicyclo[2.2.1]hept-2-ylethyl.

15

Preferably, R^{1a} is benzyl, 4-methoxybenzyl, 4-dimethylaminobutyl, 2-dimethylaminocarbonylethyl, dimethylaminocarbonylmethyl, methoxycarbonylmethyl, 3,4-dichlorobenzyl, 2-chlorobenzyl, 4-ethoxybenzyl, 4-nitrobenzyl, biphen-4-ylmethyl, naphth-1-ylmethyl, naphth-2-ylmethyl, 4-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 2-phenethyl, 4-hydroxybenzyl, 2-(4-hydroxyphenyl)ethyl, 2,6-difluorobenzyl, 2,2-difluoro-3-phenylpropyl, 2,2-dichloro-3-phenylpropyl, 2,2,2-trichloroethyl, 2,2-dichloroethyl, biphenyl-3-ylmethyl, naphth-2-yl, 3-phenylpropyl, 2,2-difluoro-3-phenylpropyl, or 2,2-dimethyl-3-phenylpropyl.

Preferably, R^{1a} is phenylmethanethiomethyl, phenylmethanesulfinylmethyl, ethylthiomethyl, ethylsulfinylmethyl, ethylsulfonylmethyl, isopropylthiomethyl, 2-methylthioethyl, 2-methylsulfinylethyl, 2-methysulfonylethyl, *tert*-butylthiomethyl, 2-fluorophenylmethane-sulfonylmethyl, 2-chlorophenylmethanesulfonylmethyl, 2-nitrophenylmethanesulfonylmethyl, 2-cyanophenylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, 2-fluorophenylmethanethiomethyl, 2-chlorophenylmethanethiomethyl, 2-cyanophenylmethanethiomethyl, 2-nitrophenylmethane-thiomethyl, cyclohexylmethanethiomethyl, cyclohexylsulfinylthiomethyl, cyclohexylmethanesulfonylmethyl,

- thiophene-2-sulfonylmethyl, 3-chloro-2-fluorophenylmethane-sulfonylmethyl, benzenesulfonylmethyl, phenylmethanesulfonylmethyl, 2-benzenesulfonylethyl, 2-(pyridin-2-ylsulfonyl)ethyl, 2-(pyridin-4-ylsulfonyl)ethyl, 2-phenylmethanesulfonyl-ethyl, oxypyridin-2-ylmethanesulfonylmethyl, 4-methoxyphenyl-methanesulfonylmethyl,
- 5 *p*-tolylmethanesulfonylmethyl, 4-chlorophenylmethanesulfonylmethyl, *o*-tolylmethanesulfonylmethyl, 3,5-dimethylphenylmethanesulfonylmethyl, 4-trifluoromethylphenylmethanesulfonylmethyl, 4-trifluoromethoxyphenylmethane-sulfonylmethyl, 2-bromophenylmethanesulfonylmethyl, naphth-2-ylmethanesulfonylmethyl, 3-methylphenylmethanesulfonylmethyl, 3-trifluoromethylphenylmethanesulfonylmethyl,
- 10 3-trifluoromethoxyphenylmethane-sulfonylmethyl, 4-fluoro-2-trifluoromethoxyphenylmethanesulfonylmethyl, 2-fluoro-6-trifluoromethylphenylmethanesulfonylmethyl, 3-chlorophenylmethanesulfonylmethyl, 2-trifluoromethylphenylmethanesulfonylmethyl, 4-*tert*-butylphenylmethanesulfonylmethyl, 2-fluoro-3-methylphenylmethanesulfonyl-methyl, 3-fluorophenylmethanesulfonylmethyl, 4-fluorophenylmethanesulfonylmethyl,
- 15 2,5-difluorophenylmethanesulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2,5-dichlorophenylmethanesulfonylmethyl, 3,4-dichlorophenylmethanesulfonylmethyl, 2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl, 3-cyanophenylmethane-sulfonylmethyl, 2-trifluoromethoxyphenylmethanesulfonylmethyl, 3-trifluoromethoxyphenylmethane-sulfonylmethyl, 2,3-difluorophenylmethane-sulfonylmethyl, 2,5-difluorophenylmethane-sulfonylmethyl, biphenyl-2-ylmethane-sulfonylmethyl, cyclohexylmethyl, 3-fluorophenylmethanesulfonylmethyl, 2-pyridin-2-ylsulfonylethyl, 2-phenylsulfonylethyl,
- 20 3,4-difluorophenylmethanesulfonylmethyl, 2,4-difluorophenylmethanesulfonylmethyl, 2,4,6-trifluorophenylmethanesulfonylmethyl, 2,4,5-trifluorophenylmethanesulfonylmethyl, 2,3,4-trifluorophenylmethanesulfonylmethyl, 2,3,5-trifluorophenylmethanesulfonylmethyl,
- 25 2,5,6-trifluorophenylmethanesulfonyl-methyl, 2-chloro-5-trifluoromethylphenylmethane-sulfonylmethyl, 2-methylpropane-1-sulfonylmethyl, 2-fluoro-3-trifluoromethylphenylmethanesulfonylmethyl, 2-fluoro-4-trifluoromethylphenylmethanesulfonylmethyl, 2-fluoro-5-trifluoromethyl-phenylmethanesulfonylmethyl, 4-fluoro-3-trifluoromethyl-phenylmethanesulfonylmethyl, 2-methoxyphenylmethanesulfonylmethyl,
- 30 3,5-bis-trifluoromethylphenyl-methanesulfonylmethyl, 4-difluoromethoxyphenylmethane-sulfonylmethyl, 3-difluoromethoxyphenylmethane-sulfonylmethyl, 2,6-dichlorophenylmethane-sulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl, 3,5-dimethyl-isoxazol-4-ylmethane-

sulfonylmethyl, 5-chlorothien-2-ylmethane-sulfonylmethyl,
2-[4-(1,1-difluoromethoxy)benzenesulfonyl]ethyl, 2-[2-(1,1-difluoromethoxy)benzene-
sulfonyl]ethyl, 2-[3-(1,1-difluoromethoxy)benzenesulfonyl]ethyl, 2-(4-trifluoromethoxy-
benzenesulfonyl)ethyl, 2-(3-trifluoromethoxybenzenesulfonyl)-ethyl, 2-(2-trifluoromethoxy-
benzenesulfonyl)-ethyl, 2-benzenesulfonylethyl, isobutylsulfanyl methyl, 2-phenylsulfanyl ethyl,
cyclohexylmethanesulfonylmethyl, 2-cyclohexylethanesulfonyl, phenylmethanesulfonylmethyl,
2-trifluoromethylphenylmetahnesulfonylmethyl, phenylsulfanyl ethyl,
cyclopropylmethanesulfonylmethyl, 2-methylpropylsulfonylmethyl, or 3,4,5-trimethoxy-
phenylmethanesulfonylmethyl, preferably 2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl.

10 Preferably, R^{1a} is 1-ethoxycarbonylpiperidin-4-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-tetrahydropyran-4-ylethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, morpholin-4-ylmethyl, 1-morpholin-4-ylethyl, thiomorpholin-4-ylmethyl, 1-oxo-thiomorpholin-4-ylmethyl, 1,1-dioxothiomorpholin-4-ylmethyl, tetrahydrothiopyran-4-ylmethyl, 1-oxotetrahydrothiopyran-4-ylmethyl, 1,1-dioxotetrahydrothiopyran-4-ylmethyl, 1-methylpiperazin-4-ylmethyl,
15 benzyloxymethyl, ethoxymethyl, isopropylloxymethyl, 2-dimethylaminoethyl, 2-piperidin-1-ylethyl, 2-pyrrolidin-1-ylethyl, *tert*-butyloxymethyl, imidazol-4-ylmethyl, indol-3-ylmethyl, 2-pyrrolidin-1-ylcarbonylethyl, pyrrolidin-1-ylcarbonylmethyl, indol-2-ylmethyl, 1-benzylimidazol-4-ylmethyl, 4-ethyl-4-methylpiperidin-1-ylmethyl, indol-1-ylmethyl, 1-methylpiperidin-2-ylmethyl, 2,2-difluoro-3-thien-2-ylmethyl, or pyridin-4-ylmethyl.

Preferred are compounds of the invention in which R^{1a} is cyclohexyl, 2-cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dichloro-3-phenylpropyl, 2,2,2-trichloroethyl, 2,2-dichloroethyl, 1,4-25 dimethylcyclopentylmethyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, 2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl, 2-(1,1-difluoromethoxy)phenylmethaneoxy-methyl, pyridin-4-ylmethyl, phenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, 2-methylpropylsulfonylmethyl,
30 cyclopropylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2-pyridin-2-ylsulfonylethyl, 2-phenylsulfonylethyl, benzyloxymethyl, 2,2-dimethylpropyl, cyclopentylmethyl, morpholin-4-ylmethyl, 5-bromothien-

2-ylmethyl, pyridin-4-ylmethyl, 2-chlorobenzyl, or 4-fluorobenzyl; most preferably 1-methylcyclopentylmethyl; and

R¹ and R² are hydrogen.

- 5 (b) Yet another more preferred group of compounds within groups (A-F) is that wherein R¹ and R^{1a} together with the carbon atoms to which they are attached form cycloalkylene or heterocycloalkylene, preferably 3,3-dimethylcyclobutyl, cyclohexyl, cyclopentyl, cyclooctyl, tetrahydrothiopyran-1,1-dioxide, or piperidin-4-yl wherein the nitrogen atom at the 1-position of the piperidinyl ring is optionally substituted with R^f where R^f is alkyl or -SO₂R where R is alkyl,
- 10 cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl where the rings in R^f are optionally substituted with one, two, or three substituents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, halo, or carboxy.

- (1) Within the above preferred, more preferred, and even more preferred groups above, a particularly preferred group of compounds is that wherein:

15 R³ is hydrogen, alkyl, cycloalkyl, phenyl, benzyl, naphthyl, alkylSO₂alkyl, cycloalkylSO₂alkyl, arylSO₂alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl,

20 benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoisoxazolyl, benzoxazolyl, amino, alkylamino, or dialkylamino; wherein the aromatic or alicyclic ring in R³ is optionally substituted by one, two, or three R⁸;

each R⁸ is independently alkyl, halo, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, cycloalkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, alkoxy, -COR (where R is alkyl), -OC(O)R (where R is alkoxy or aryl), aryloxy, benzyloxy, alcoxycarbonyl, aryloxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl,

30 pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or

- quinoxalinyl, -NHCOR (where R is alkyl or aryl), alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkoxy carbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, or amino wherein the nitrogen atom may be independently mono or
 - 5 di-substituted by alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, where the aromatic or alicyclic rings in R^g may be further optionally substituted by one, two or three R^h independently selected from alkyl, alkoxy,
 - 10 haloalkyl, haloalkoxy, halo, hydroxy, carboxy, carboxamido, cyano, nitro, aryl or cycloalkyl;
 - R² is hydrogen or methyl;
 - R⁴ is hydrogen, hydroxy, nitrile, -(alkylene)-X⁶-R³⁸ (where X⁶ is -O-, -NR³⁹-, -S(O)_{n7}-, -NR³⁹CO-, -CO-, or -OC(O)- where R³⁹ is hydrogen or alkyl and R³⁸ is hydrogen, alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolyl, pyranlyl,
 - 15 thiopyranlyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl, or quinoxalinyl; and
 - R^{4a} is hydrogen, alkyl, cycloalkyl, aminoalkyl, aryl, alkoxy, aryloxy, benzyloxy, or -C(O)OR where (R is hydrogen, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl,
 - 20 heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroaralkyl, aryl, or aralkyl).
- Preferably, R³ is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl, or amino where the nitrogen atom is mono or disubstituted with alkyl, and wherein the aromatic or alicyclic rings in R³ are optionally substituted with one, two, or three R^g independently selected from methyl, ethyl, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, phenoxy carbonyl, carbamoyl wherein the nitrogen atom is mono or disubstituted independently with methyl, ethyl or phenyl, acetyl amino, benzoyl amino, methylthio, phenylthio, phenylsulfonyl, methylsulfonyl, methoxycarbonylamino, phenoxy carbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, or amino wherein the nitrogen

- atom is mono or disubstituted independently with methyl or phenyl; wherein the aromatic or alicyclic rings in R^g are further optionally substituted with one, two, or three R^h independently selected from methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro, hydroxy, carboxy, or carboxamido.
- 5 Even more preferably, R³ is hydrogen, methyl, carboxy, ethyl isopropyl, cyclopropyl, cyclohexyl, phenyl, naphthyl, benzyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino where the nitrogen atom is mono or disubstituted with alkyl and wherein the aromatic or alicyclic rings in R³ are optionally substituted with one, two, or three R^g independently selected from methyl, fluoro, chloro, phenyl,
- 10 thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, carbamoyl wherein the nitrogen atom is mono or disubstituted independently with methyl or phenyl, acetylamino, methylthio, phenylthio, phenylsulfonyl, methylsulfonyl, methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom is mono or disubstituted independently with methyl or phenyl. Most
- 15 preferably, R³ is hydrogen, isopropyl, cyclohexyl, phenyl, 4-(acetylamino)phenyl, 4-methanesulfonylaminophenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, thiomorpholinyl, furanyl, thienyl, pyridin-4-yl, pyrazinyl, methylamino, ethylamino, dimethylamino or diethylamino.
- 20 Within the above preferred and more preferred R³ groups, R⁴ is hydrogen and R^{4a} is hydrogen, alkyl or alkoxy; preferably, hydrogen; or
- R^{4a} is -C(O)OR, preferably ethoxycarbonyl, 2-methylpropyloxycarbonyl, 2,2,-dimethylpropyloxy-carbonyl, methoxycarbonyl, cyclopentyloxycarbonyl, propyloxycarbonyl,
- 25 hexyloxycarbonyl, 3-methoxybutyloxycarbonyl, 2-isobutyloxy-ethyloxycarbonyl, isopropyloxycarbonyl, benzyloxycarbonyl, cyclohexylmethyloxy-carbonyl, pyran-4-ylmethyloxycarbonyl, tetrahydrofuran-3-yloxycarbonyl, 2-methoxyethoxycarbonyl, 3,3,3-trifluoropropyloxycarbonyl, cyclobutylmethyloxycarbonyl, cyclobutoxycarbonyl, piperidin-4-ylmethoxycarbonyl, 3-pyrrolidin-1-ylpropyloxycarbonyl, 3-piperidin-1-ylpropyloxycarbonyl, 3-
- 30 dimethylpropyl-oxycarbonyl, 2-dimethylaminoethyloxycarbonyl, 2-pyridin-4-ylethyloxy-carbonyl, or 2-(4-methylpiperazin-1-ylethyloxy)carbonyl.

(2) Within the above preferred, more preferred, and even more preferred groups above, yet another particularly preferred group of compounds is that wherein:

R² and R^{4a} are hydrogen;

5 R³ is hydrogen, alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, pyridinyl, or amino; wherein R³ is optionally substituted by one, two or three R⁸ where each R⁸ is independently halo or alkyl. Preferably, R³ is methyl, trifluoromethyl, 2,2,2-trifluoroethylamino, amino, N,N-dimethylamino, morpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperazin-1-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-10 yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, pyrimidin-4-yl, oxazol-4-yl, oxazol-5-yl, thiazol-4-yl, thiazol-5-yl, quinolin-6-yl, indol-5-yl, 2-methylimidazol-4-yl, phenyl, or 4-fluorophenyl; and

15 R⁴ is hydrogen, alkyl, or halogenated alkyl, preferably, hydrogen, 2,2,2-trifluoroethyl or methyl.

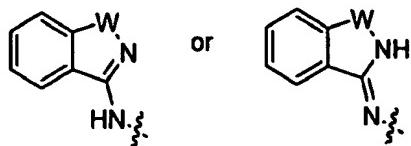
15 (3) Within the above preferred, more preferred, and even more preferred groups above, yet another particularly preferred group of compounds is that wherein:

R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a 5, 6, or 7 membered heterocycloalkyl ring, preferably a heterocycloalkyl ring containing at least an -SO₂- group or a 5, 6, or 7 membered heterocycloalkyl ring containing at least an -SO₂- group that is fused to an aryl or heteroaryl ring wherein each ring is optionally independently substituted by one or two R^j where each R^j is independently halo, alkoxy, haloalkyl, haloalkoxy, hydroxy or alkyl.

25 More preferably, R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a 5 or 6 membered heterocycloalkyl ring containing at least an -SO₂- group or a 5 or 6 membered heterocycloalkyl ring containing at least an -SO₂- group and is fused to a thienyl or pyrrolyl ring optionally independently substituted by one or two R^j.

30 Even more preferably, R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a 5 or 6 membered heterocycloalkyl ring containing at least an -SO₂- group or a 5 or 6 membered heterocycloalkyl ring containing at least an -SO₂- group and is fused to a phenyl or pyridinyl ring optionally independently substituted by one or two R^j.

35 Most preferably, R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a ring of formula:



wherein W is $-S(O)_2-$ wherein each ring is optionally independently substituted by one or two R^j where each R^j is independently chloro, fluoro, methoxy, trifluoromethyl, trifluoromethoxy, hydroxy, or methyl.

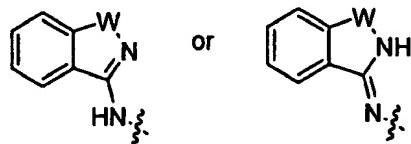
Within the above preferred and more preferred groups in (3), a particularly preferred group of compounds is that where R² is hydrogen.

(4) Within the above preferred, more preferred, and even more preferred groups above, yet another particularly preferred group of compounds is that wherein:

R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a 5, 6, or 7 membered heterocycloalkyl ring fused to an aryl or heteroaryl ring wherein said heterocyclic ring is substituted on the aromatic and/or non-aromatic portion of the rings with one, two, or three R^j provided that the heterocycloalkyl ring does not contain an $-SO_2-$ group;

each R^j is independently alkyl, cycloalkyl, aryl, alkoxy, aryloxy, benzyloxy, alkoxycarbonyl, where each of the aforementioned groups is optionally substituted with halo, haloalkyl, alkyl, alkoxy, haloalkoxy, hydroxy, oxo, carboxy, nitrile, nitro, or $-C(O)NH_2$.

Most preferably, R³ and R⁴ in (Ia) and (Ib) together with the atoms to which they are attached form a ring of formula:



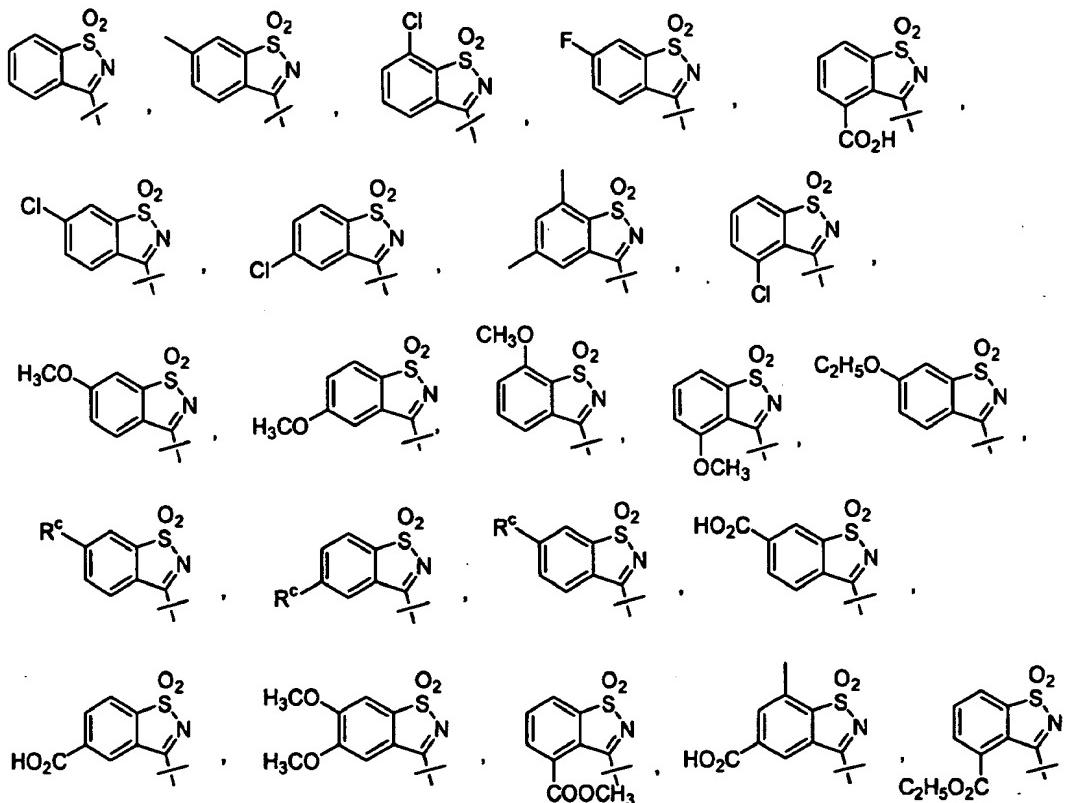
wherein W is $-O-C(O)-$, $-CO-$, or $-NR-C(O)-$ (where R is hydrogen, alkyl, alkoxycarbonylalkyl, alkylsulfonylalkyl, alkylaminoalkyl, di-alkylaminoalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl), wherein each ring is independently substituted by one or two R^j

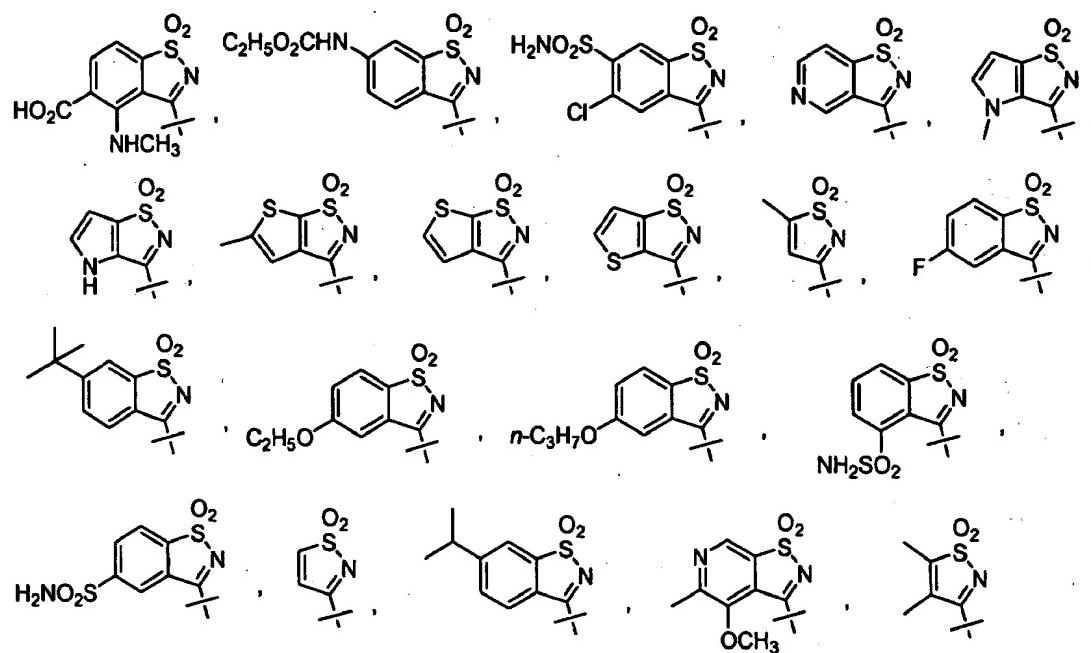
each R^j is independently chloro, fluoro, methoxy, trifluoromethyl, trifluoromethoxy, hydroxy, methyl, or phenyl where the phenyl ring is optionally substituted with one, two or three

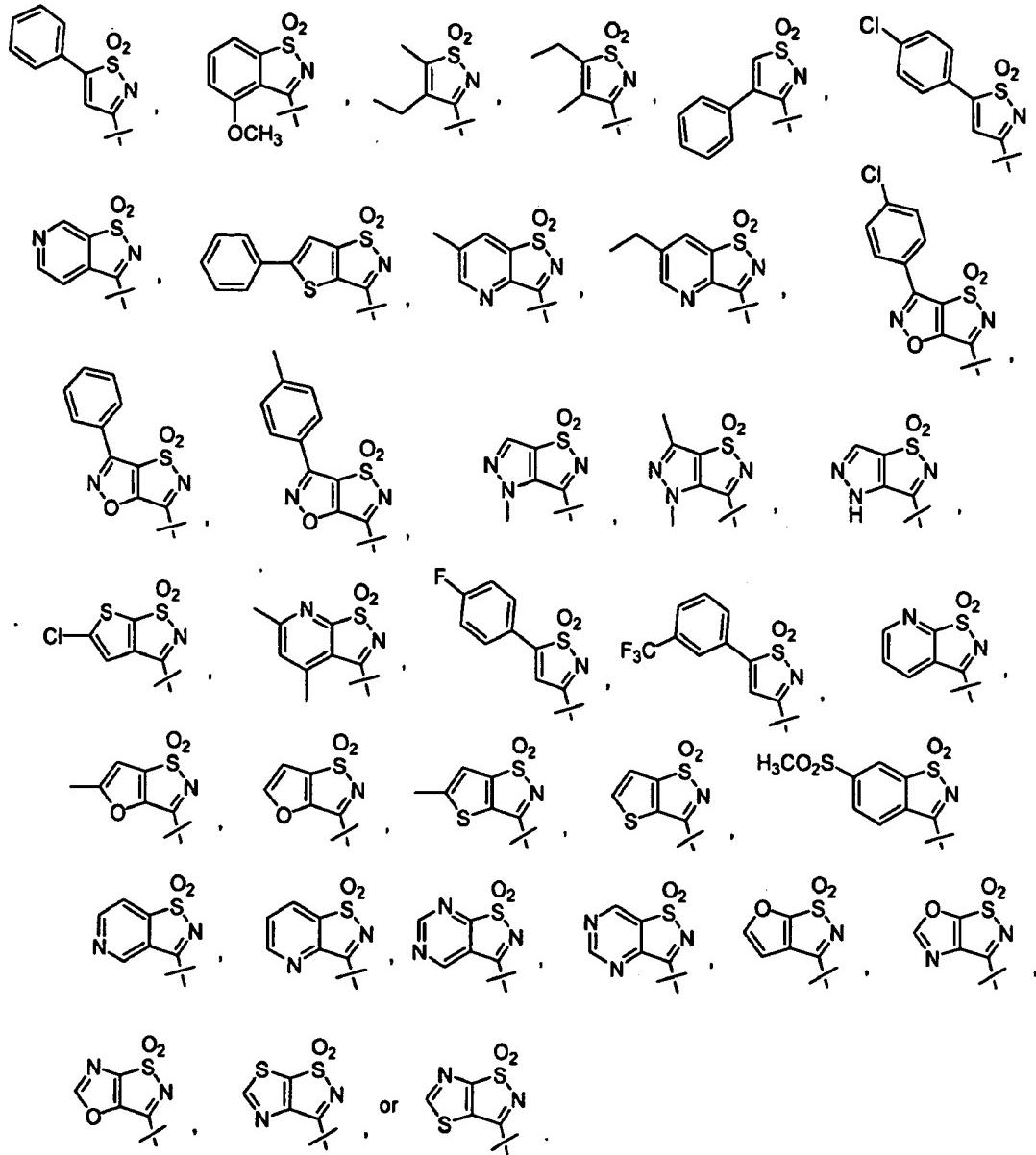
substituents independently selected from chloro, fluoro, methyl, methoxy, trifluoromethyl, trifluoromethoxy, or hydroxy. Preferably R^j is phenyl where the phenyl ring is optionally substituted with one, two or three substituents independently selected from chloro, fluoro, methyl, methoxy, trifluoromethyl, trifluoromethoxy, or hydroxy.

5 Within the above preferred and more preferred groups in (4), a particularly preferred group of compounds is that where R² is hydrogen.

(5) Within the above preferred, more preferred and even more preferred groups, yet another particularly preferred group of compounds is that wherein R³ and R⁴ together with the atoms to which they are attached form a group selected from:



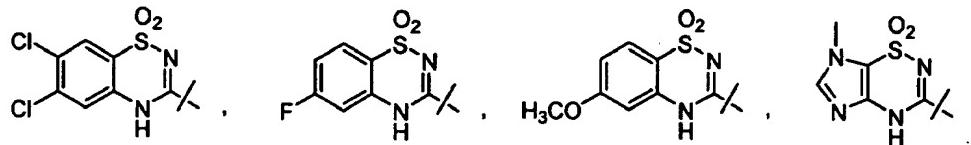
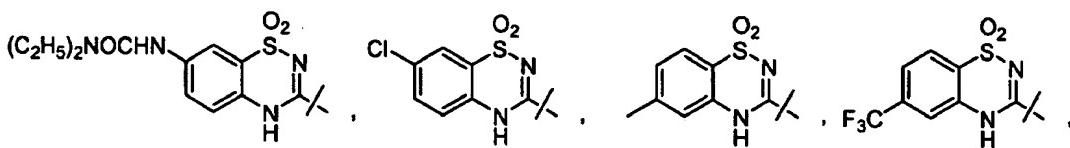
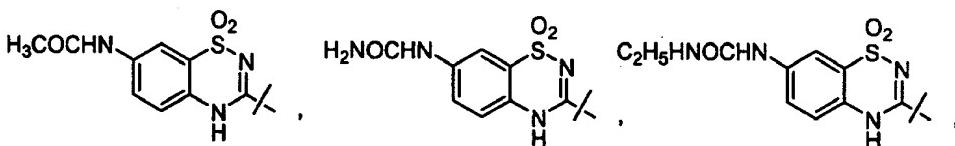
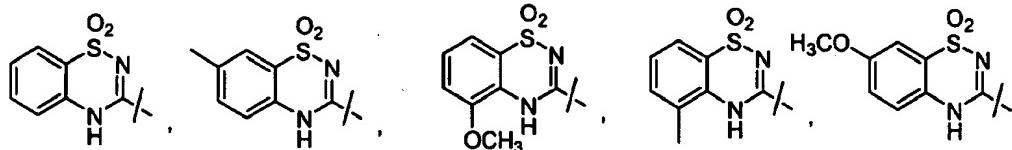
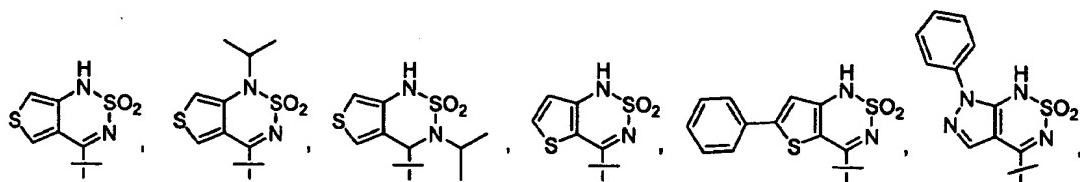
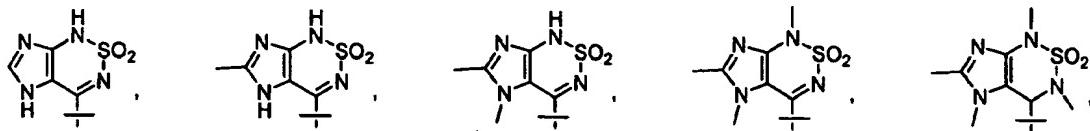
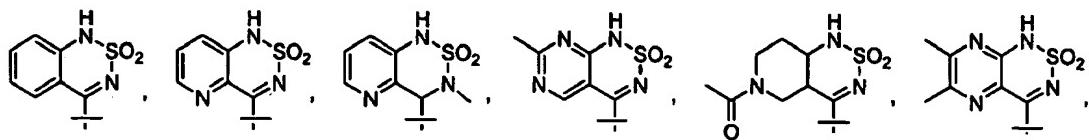


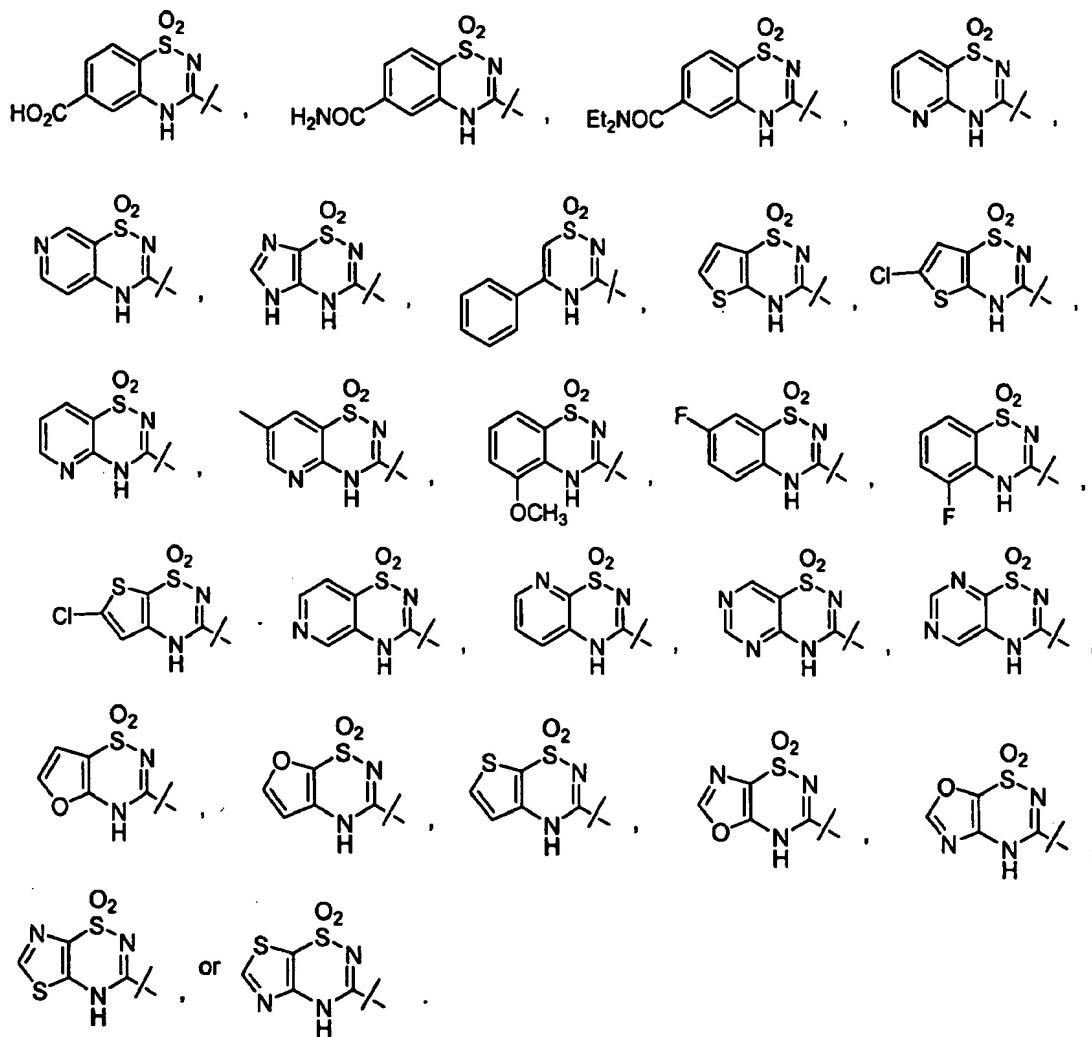


where R^c is amino, methylsulfonylamino, ethylsulfonylamino, methylamino, dimethylamino, acetylarnino, methoxy, ethoxy, methylaminocarbonyl, aminocarbonyl, diethylaminocarbonyl, dimethylaminocarbonyl, methylaminocarbonyl, or ethoxycarbonylamino.

5 Within the above preferred and more preferred groups in (7), a particularly preferred group of compounds is that where R² is hydrogen.

(6) Within the above preferred, more preferred and even more preferred groups, yet another particularly preferred group of compounds is that wherein R³ and R⁴ together with the atoms to which they are attached form a group selected from:





In the above groups, the hydrogen atom attached to the nitrogen can be replaced by alkyl, haloalkyl, (preferably, methyl, ethyl, propyl, isopropyl, *n*-, *iso*-, or *tert*-butyl, or trifluoromethyl), 5 methylsulfonylmethyl, methoxycarbonylmethyl, 2-methylsulfonylethyl, 2-methoxycarbonylethyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylpiperidin-4-yl, 1-methylpiperidin-4-ylmethyl, 2-(1-methylpiperazin-4-yl)ethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyridin-4-ylethyl, 3-pyrrolidin-1-ylpropyl, 3-piperidin-1-ylpropyl, 2,2,2-trifluoroethyl, or 2-morpholin-4-ylethyl.

Within the above preferred and more preferred groups in (6 and 7), a particularly preferred 10 group of compounds is that where R² is hydrogen.

A person skilled in the art will recognize that compounds of Formula (Ia) where R² is hydrogen can tautomerize to give a compound of Formula (Ib) where R⁴ or R^{4a} is hydrogen and compounds of Formula (Ib) where R⁴ or R^{4a} is hydrogen can tautomerize to give a compound of Formula (Ia) or (Ib') respectively, where R² is hydrogen. Such tautomers are within the scope of

* this group. The amount of each tautomer present will depend on various conditions such as steric hinderance, pH, temperature, and the like. Accordingly, this group encompasses individual tautomeric forms of compounds of Formula (Ia) as well as mixtures thereof.

5 (II). Another preferred group of compounds is represented by Formula (II).

Within this group (II), a more preferred group of compounds is that wherein E and R^{1a} are as defined in (I) above, R¹ and R² are hydrogen and Z is -CO-.

Within these groups of compound, a more preferred group of compounds is that wherein Q is -CO-.

10

Within these groups of compound, another more preferred group of compounds is that wherein Q is -OCO-.

15 Within these groups of compound, yet another more preferred group of compounds is that wherein Q is -NHCO-.

Within these preferred and more preferred groups, an even more preferred group of compounds is that wherein R^{3c} is alkyl, -alkylene-C(O)OR⁴⁰, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl wherein said 20 cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is optionally substituted with one or two R^k.

Within the above preferred, more preferred groups, a particularly preferred group of compounds is that wherein R^{3c}-Q is a group selected from acetyl, azetidin-3-ylcarbonyl, benzyloxycarbonyl, 1-benzyloxycarbonylpiperidin-4-ylcarbonyl, benzylsulfonyl, bicyclo[2.2.2]hept-2-ylcarbonyl, bicyclo[2.2.1]hept-2-ylcarbonyl, *tert*-butoxycarbonyl, 25 carboxyacetyl, 2-carboxypropionyl, 3-carboxypropionyl, 2-cyclohexylacetyl, 4-cyclohexylbutyryl, 2-cyclohexylethylsulfonyl, cyclohexylmethoxycarbonyl, 3-cyclohexylpropionyl, 2-cyclopentylethylsulfonyl, 3-cyclopentylpropionyl, di(2-methoxyethyl)carbamoyl, dimethylcarbamoyl, 6-hydroxypyrid-3-ylcarbonyl, 1*H*-imidazol-4-ylcarbonyl, methoxycarbonyl, methylsulfonyl, 4-methylvaleryl, morpholin-4-ylcarbonyl, 2-morpholin-4-ylethylcarbonyl, 30 naphth-1-ylacetyl, naphth-1-ylmethylcarbonyl, 3-phenylpropionyl, piperazin-1-ylcarbonyl, piperidin-4-ylcarbonyl, pyrazin-2-ylcarbonyl, pyridin-3-ylcarbonyl, pyridin-4-ylcarbonyl, pyridin-3-ylaminocarbonyl, tetrahydropyran-4-ylcarbonyl, and tetrahydropyran-4-yloxycarbonyl.

- R^{3c}-Q- particularly represents acetyl, benzoyl, benzyloxycarbonyl, benzylsulfonyl, bicyclo[2.2.2]hept-2-ylcarbonyl, *tert*-butoxycarbonyl, *tert*-butyryl, 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyl, 1-*tert*-butoxycarbonylpiperidin-4-ylcarbonyl, 2-cyclohexylacetyl, 4-cyclohexylbutyryl, 2-cyclohexylethylsulfonyl, 3-cyclohexylpropionyl,
- 5 2-cyclopentylethylsulfonyl, 4-methylpiperazin-1-ylcarbonyl, methylsulfonyl, 4-methylvaleryl, 3-morpholin-4-ylpropionyl, naphth-2-ylmethyl, 3-phenylpropionyl, piperazin-1-ylcarbonyl, piperidin-4-ylcarbonyl or pyridin-3-ylcarbonyl, wherein within R^{3c} any alicyclic or aromatic ring system present may be substituted further by 1 to 3 radicals independently selected from 3-aminomethyl and 3-*tert*-butoxycarbonylaminomethyl.
- 10 R^{3c}-Q- especially represents morpholin-4-ylcarbonyl, methoxycarbonyl, methylsulfonyl, piperidin-4-ylcarbonyl, pyrazin-2-ylcarbonyl pyridin-3-ylcarbonyl, pyridin-4-ylcarbonyl, tetrahydropyran-4-ylcarbonyl or tetrahydropyran-4-yloxycarbonyl.

(III). Another preferred group of compounds is represented by Formula (III).

- 15 Within this group (III), a more preferred group of compounds is that wherein E is as defined in (I) above.

Within these preferred groups, a more preferred group of compounds is that wherein:

- R^{3d} and R^{3e} are independently -(alkylene)-X⁹-R⁴³, wherein X⁹ is bond, -S-, -O-, -C(O)-, -CONR⁴⁴-, -NR⁴⁴SO₂-, or -SO₂- where R⁴⁴ is hydrogen or alkyl and R⁴³ is alkyl, haloalkyl,
- 20 cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic rings in R^{3d} and R^{3e} are optionally substituted with one, two or three R^m independently selected from alkyl, cyano, halo, haloalkyl, haloalkoxy, alkylcarbamoyloxy, hydroxy, alkoxy, carboxy, alkoxy carbonyl, acyl, carbamoyl, alkylsulfonylamino, and alkylsulfonyl, and one substituent selected from aryl, aralkyl, heteroaryl,
- 25 heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl optionally substituted with one to three Rⁿ.

- Preferably, R^{3d} and R^{3e} are independently benzylcarbamoyl-methyl, benzyl, benzylsulfonylmethyl, 2-benzenesulfonylethyl, benzenesulfonylmethyl, 2-benzo[1,3]dioxol-5-yl-2-oxo-ethyl, 2-benzo[b]thiophen-2-yl-2-oxo-ethyl,
- 30 biphenyl-2-ylmethylsulfonylmethyl, biphenyl-4-ylmethyl-sulfonylmethyl, biphenyl-3-ylmethyl, biphenyl-4-ylmethyl, 2-biphenyl-4-yl-2-oxo-ethyl, 3,5-bis-trifluoromethylbenzylsulfonylmethyl, 3-bromo-benzyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-bromobenzylsulfonylmethyl,

- (butylmethylcarbamoyl)methyl, 4-*tert*-butyl-benzylsulfonylmethyl, (3-carbamoylphenylcarbamoyl)methyl, (4-carbamoylphenylcarbamoyl)methyl, 4-carboxybenzylsulfonylmethyl, 2-(3-chloro-benzo[*b*]thiophen-2-yl)-2-oxo-ethyl, 2-(4'-chlorobiphenyl-4-yl)-2-oxo-ethyl, 3-chloro-2-fluoro-benzylsulfonylmethyl, 2-chlorobenzylsulfonylmethyl,
- 5 3-chlorobenzylsulfonylmethyl, 4-chlorobenzylsulfonylmethyl, 2-(4-chlorophenyl)-2-oxo-ethyl, 5-chlorothiophen-2-ylmethylsulfonylmethyl, 2-(3-chlorothiophen-2-yl)-2-oxo-ethyl, 2-chloro-5-trifluoromethylbenzylsulfonylmethyl, cyclohexylcarbamoylmethyl, 2-cyclohexylethyl, cyclohexylmethyl, 2-cyanobenzylsulfonylmethyl, cyclopropylmethylsulfonylmethyl,
- 10 3-cyanobenzylsulfonylmethyl, 4-cyanobenzylsulfonylmethyl, 2,5-dichlorobenzylsulfonylmethyl, 2,6-dichlorobenzylsulfonylmethyl, 3,4-dichlorobenzylsulfonylmethyl, 2-[2-(1,1-difluoromethoxy)benzenesulfonyl]-ethyl, 2-[3-(1,1-difluoromethoxy)benzenesulfonyl]ethyl, 2-[4-(1,1-difluoromethoxy)-benzenesulfonyl]-ethyl, 2-(1,1-difluoromethoxy)-benzylsulfonylmethyl, 3-(1,1-difluoromethoxy)-benzylsulfonylmethyl, 4-(1,1-difluoromethoxy)-benzylsulfonylmethyl,
- 15 2,3-difluoro-benzylsulfonylmethyl, 2,4-difluoro-benzylsulfonylmethyl, 2,5-difluorobenzylsulfonylmethyl, 2,6-difluorobenzylsulfonylmethyl, 3,4-difluoro-benzylsulfonylmethyl, 3,4-dichlorobenzyl-sulfonylmethyl, 2-(3,4-difluorophenyl)-2-oxo-ethyl, 2-(3,4-dimethoxyphenyl)-2-oxo-ethyl, 4-dimethylcarbamoylmethyl, 3,5-dimethylisoxazol-4-ylmethylsulfonylmethyl, 3,5-dimethylbenzylsulfonylmethyl, 2-(3-fluoro-4-methoxyphenyl)-2-oxo-ethyl,
- 20 2-fluoro-3-methylbenzylsulfonylmethyl, 2-fluorobenzylsulfonylmethyl, 3-fluorobenzylsulfonylmethyl, 4-fluorobenzylsulfonylmethyl, 2-(4-fluorophenyl)-2-oxo-ethyl, 4-fluoro-2-trifluoromethoxybenzylsulfonylmethyl, 2-fluoro-3-trifluoromethylbenzylsulfonylmethyl, 2-fluoro-4-trifluoromethylphenylmethylsulfonylmethyl, 2-fluoro-5-trifluoromethylbenzyl-sulfonylmethyl, 2-fluoro-6-trifluoromethyl-benzylsulfonylmethyl,
- 25 4-fluoro-3-trifluoromethylbenzylsulfonylmethyl, 2-(4-hydroxyphenyl)-2-oxo-ethyl, isobutylsulfanyl methyl, isopropylcarbamoylmethyl, 2-(4-methylsulfonylamino-phenyl)-2-oxo-ethyl, 2-(4-methylsulfonyl-piperazin-1-yl)-2-oxo-ethyl, 5-methyl-2-oxo-hexyl, 2-methoxybenzylsulfonylmethyl, 4-methoxybenzylsulfonylmethyl, 2-(4-methoxyphenyl)-2-oxo-ethyl, 3-methylbenzylsulfonylmethyl, 2-methylpropane-1-sulfonylmethyl,
- 30 2-(5-methylthiophen-2-yl)-2-oxo-ethyl, 2-methylthiazol-4-yl-methylsulfonylmethyl, 5-methylthiophene-2-sulfonylmethyl, naphthalen-2-ylmethylsulfonylmethyl, 2-naphthalen-2-yl-2-oxo-ethyl, naphthalene-2-sulfonylmethyl, 2-morpholin-4-yl-2-oxo-ethyl,

- 2-oxo-2-piperidin-1-ylethyl, 2-oxo-2-phenylethyl, 2-oxo-2-pyrrolidin-1-ylethyl,
 2-oxo-2-thiophen-2-ylethyl, 2-oxo-2-thiophen-3-ylethyl, 2-oxo-2-*p*-tolylethyl,
 2-oxo-2-(4-trifluoromethoxyphenyl)-ethyl, 1-oxy-pyridin-2-ylmethylsulfonylmethyl,
 phenylcarbamoylmethyl, 2-benzylsulfonylethyl, 4-benzylsulfonylmethyl, 2-phenylsulfanylethyl,
 5 pyridin-3-ylcarbamoylmethyl, pyridin-4-ylcarbamoylmethyl, 2-(pyridin-2-sulfonyl)-ethyl,
 2-(pyridin-4-sulfonyl)-ethyl, pyridin-2-ylmethylsulfonylmethyl,
 pyridin-3-ylmethylsulfonylmethyl, pyridin-4-ylmethylsulfonylmethyl, tetrahydropyran-4-
 yloxymethyl, thiophene-2-sulfonylmethyl, *o*-tolylmethylsulfonylmethyl,
m-tolylmethylsulfonylmethyl, *p*-tolylmethylsulfonylmethyl, 2-(2-trifluoromethoxy-
 10 benzenesulfonyl)-ethyl, 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl,
 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-trifluoromethoxy-benzylsulfonylmethyl,
 2-trifluoromethoxy-benzylsulfonylmethyl, 3-trifluoromethoxy-benzylsulfonylmethyl,
 4-trifluoromethoxy-benzylsulfonylmethyl, 2-trifluoromethyl-benzylsulfonylmethyl,
 2-trifluoromethyl-benzylsulfonylmethyl, 3-trifluoromethyl-benzylsulfonylmethyl,
 15 4-trifluoromethyl-benzylsulfonylmethyl, 2,3,4-trifluoro-benzylsulfonylmethyl,
 2,3,5-trifluoro-benzylsulfonylmethyl, 2,4,5-trifluoro-benzylsulfonylmethyl,
 2,4,6-trifluoro-benzylsulfonylmethyl and 2,5,6-trifluoro-benzylsulfonylmethyl. Preferred R^{3d} and
 R^{3e} groups are benzylsulfanylmethyl, 3-cyano-benzyl-sulfonylmethyl, cyclohexylmethyl,
 2-difluoromethoxy-benzylsulfonylmethyl, isobutylsulfanylmethyl, (2-methyl-thiazol-4-yl)-
 20 methylsulfonylmethyl, 2-morpholin-4-yl-2-oxo-ethyl, 2-oxo-2-piperidin-1-yl-ethyl,
 2-oxo-2-pyrrolidin-1-yl-ethyl, benzylsulfonylmethyl, tetrahydropyran-4-yloxymethyl, and
 3-trifluoromethyl-benzylsulfonylmethyl. Particularly preferred R^{3d} and R^{3e} groups are
 benzylsulfanylmethyl, 2-difluoromethoxy-benzylsulfonylmethyl, 2-morpholin-4-yl-2-oxo-ethyl
 and benzylsulfonylmethyl.
 25

(IV). Another preferred group of compounds is represented by Formula (IV).

Within this group (IV), a more preferred group of compounds is that wherein E and R^{1a} are as defined in (I) above.

Within the preferred and more preferred groups, an even more preferred group of compounds is that wherein R^{3g} is -OH or -OC(O)NR⁴⁹R⁵⁰, preferably wherein R⁴⁹ is hydrogen, alkyl, hydroxalkyl, alkoxyalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl and R⁵⁰ is hydrogen or alkyl or R⁴⁹ and

- R^{50} together with the nitrogen atom to which both R^{49} and R^{50} attached form a heterocycloalkyl ring, which ring may be unsubstituted or substituted with hydroxy, alkylsulfonyl, alkoxy carbonyl, aralkyl, or acyl. Preferably, R^{3g} is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy,
- 5 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-benzyl-carbamoyloxy, pyrrolidin-1-yl-carbonyloxy, piperidin-1-yl-carbonyloxy, 4-methanesulfonyl-piperazin-1-yl-carbonyloxy, 4-ethoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-cyclohexyl-carbamoyloxy, *N*-phenyl-carbamoyloxy, *N*-butyl-*N*-methyl-carbamoyloxy, *N*-pyridin-3-yl-carbamoyloxy, *N*-isopropyl-carbamoyloxy, *N*-pyridin-4-yl-carbamoyloxy, *N,N*-bis-(2-methoxy-ethyl)-carbamoyloxy, *N*-
- 10 phenethyl-carbamoyloxy, piperazinecarbonyloxy, *N*-naphthalen-2-yl-carbamoyloxy, 4-benzyl-piperazin-1-ylcarbamoyloxy, 4-(1-furan-2-yl-carbonyl)-piperazin-1-ylcarbamoyloxy, thiomorpholin-4-ylcarbonyloxy, 1,1-dioxo-1 λ^6 -thiomorpholin-4-ylcarbonyloxy, morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydrofuran-2-ylmethylcarbamoyloxy,
- 15 cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxypyrrolidin-1-ylcarbonyloxy and carbamoyloxy. More particularly, R^{3g} is morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy or
- 20 carbamoyloxy.

Another more preferred group of compounds is that wherein R^{3g} is $-NHR^{48}$ wherein R^{48} is aryl or heteroaryl or $-NR^{47}R^{48}$ wherein R^{47} is heterocycloalkyl and R^{48} is hydrogen or alkoxyalkyl, or R^{47} and R^{48} independently are aralkyl or heteroaralkyl, wherein within R^{47} and R^{48} any alicyclic or aromatic ring system is optionally substituted with one, two, or three R^q independently selected from alkyl, cyano, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, carboxyl, alkoxy carbonyl, acyl, carbamoyl, or alkylsulfonylamino. Preferably, R^{3g} is selected from 5-nitrothiazol-2-ylamino, 2-nitrophenylamino, pyrimidin-2-ylamino, tetrahydropyran-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydropyran-4-yl)amino, 1-methyl-piperidin-4-ylamino,

25 30 isopropylamino, di(thien-2-ylmethyl)amino or di(benzyl)amino.

Yet another more preferred group of compounds is that wherein R^{3g} is $-OR^{46}$ wherein R^{46}

- is 4-methoxy-phenyl, 4-hydroxymethyl-phenyl, methoxymethyl, phenyl-methanoyl, 1-(4-phenoxy-phenyl)-methanoyl, 3-biphenyl, 4-biphenyl, 1-biphenyl-4-yl-methanoyl, naphthalen-2-yl-methanoyl, benzo[1,3]dioxol-5-yl-methanoyl, (4-methanesulfonylaminophenyl)methanoyl, benzo[b]thien-2-yl-methanoyl, 4'-chloro-4-biphenyl, 4-hydroxyphenylmethanoyl, 3-chloro-5-benzo[b]thien-2-yl-methanoyl, thien-2-yl-methanoyl, thien-3-ylmethanoyl, 3-chlorothien-2-yl-methanoyl, 5-methylthien-2-ylmethanoyl, 4-methoxyphenylmethanoyl, 4-trifluoromethoxyphenylmethanoyl, 4-chlorophenylmethanoyl, 3-bromophenyl, cyclohexylmethyl, 3,4-dimethoxyphenylmethanoyl, 3,4-difluorophenylmethanoyl, 3-fluoro-4-methoxyphenylmethanoyl, 4-fluorophenylmethanoyl, 4-trifluoromethylphenylmethanoyl, 4-formylphenylformyl, 3-formylphenylformyl, 4-methylpentanoyl, tetrahydropyran-4-ylmethyl, or 2-morpholin-4-yl-2-oxo-ethyl.

Most particularly preferred are compounds of the invention where R^{3g} is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, N-(2-methoxyethyl)-N-(tetrahydro-pyran-4-yl)amino, isopropylamino, and 15 cyclohexylamino.

Additionally, in the preferred embodiments above, a number of different preferences have been given above, and following any one of these preferences results in a compound of this invention that is more presently preferred than a compound in which that particular preference is not followed. However, these preferences are generally independent; and 20 following more than one of these preferences may result in a more presently preferred compound than one in which fewer of the preferences are followed.

GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes 25 shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic 30 Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons,

4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

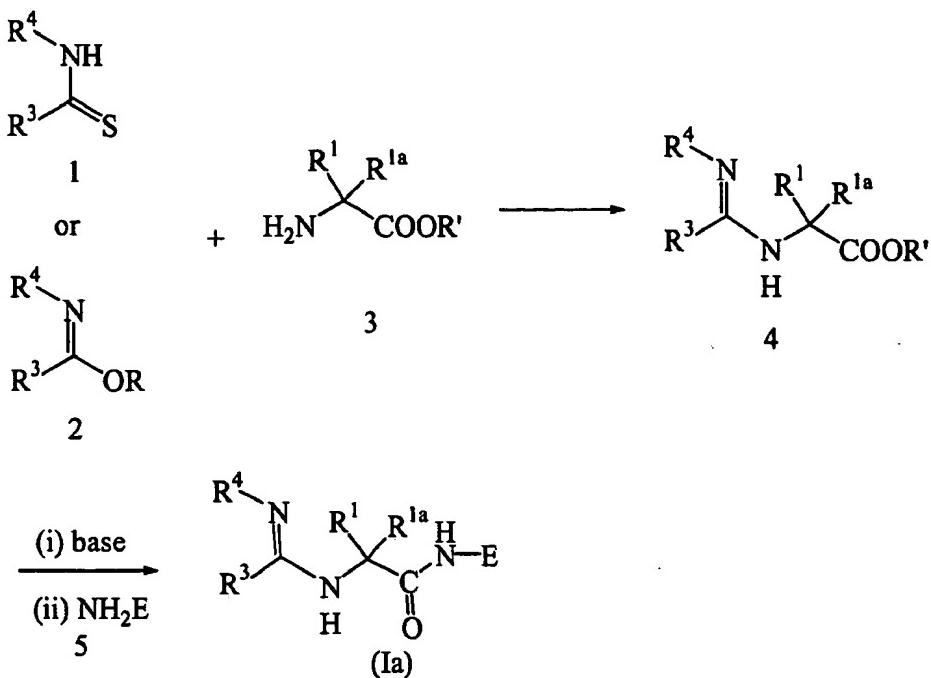
5 The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

10 Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

15 In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "*Protective Groups in Organic Chemistry*" John Wiley and Sons, 1991. Compound of Formula (Ia) and (Ib) can be prepared by the procedures described in Schemes 1-4 below.

20 Compounds of Formula (Ia) where E is -C(R⁵)(R⁶)X¹ or -C(R^{5a})(R^{6a})CN and R¹, R^{1a}, R², R³, R⁴, R⁵, R^{5a}, R⁶ and R^{6a} are as defined in the Summary of the Invention can be prepared as shown in Scheme 1 below.

Scheme 1



Compounds of Formula (Ia) can be prepared by reacting an amino acid derivative of formula 3 where R' is alkyl, with a thione of formula 1 to give a compound of formula 4. The reaction is carried out in the presence of a suitable coupling agent such as 2-chloro-1-methylpyridinium iodide (Yong, Y. F., et. al., *J. Org. Chem.* 1997, 62, 1540), phosgene or triphosgene (Barton, D. H., et. al., *J. Chem. Soc. Perkin Trans. I*, 1982, 2085), alkyl halides (Brand, E and Brand, F. C., *Org. Synth.*, 1955, 3, 440), or carbodiimide (Poss, M. A., et. al., *Tet. Lett.*, 1992, 40, 5933).

Alternatively, a compound of formula 4 is prepared by reacting a hydroxy compound of formula 2 with an amino acid derivative of formula 3. The reaction is carried out optionally in the presence of a base such as triethylamine. Suitable reaction conditions are known to those skilled in the art and examples of such amine additions can be found in the art e.g., Haake, M., et. al., *Synthesis*, 1991, 9, 753; Dauwe, C., et al, *Synthesis*, 1995, 2, 171, Reid, et. al., *Justus Liebigs Ann. Chem.*, 1966, 97, 696; and Dean N. D., and Papadopoulos, E.P. *J. Het. Chem.*, 1982, 19, 1117.

Compounds of formula 1 are commercially available or they can be prepared by methods well known in the art. For example, *N*-phenyl-2,2,2-trifluorothioacetamide can be prepared by method described in *Tet. Lett.*, 2001, 42, 46, 8181-8184; *N*-thiazol-2-ylthioacetamide can be prepared by the procedure described in *Chem. Heterocyclo*, 1972, 848-851; and *N*-thiazol-2-ylphenylthiobenzamide can be prepared as described in by the procedure described in *Chem. Heterocyclo*, 1988, 337-344. Others can be prepared by methods are described in PCT

- Application Publication No. WO 02/20485 the disclosure of which is incorporated herein by reference in its entirety. Compounds of formula 2 are either commercially available or they can be prepared by methods known in the art. Some such methods are described in Francesconi, I., et al., *J. Med. Chem.*, 1999, 42, 2260; Kurzer, F., et. al., *Org. Synth.* 1963, 645; and Futman, A. D., U. S Patent No.3,984,410. For example, ethyl benzenesulfonyl formimidate can be prepared by methods described in Stetter, H. and Theisen, D. H. *Chem Ber.*, 1969, 102, 1641-42 and Ortiz, J. A., *Arzneim.-Forsch./Drug Res*, 1977, 47, 431-434.

Amino acids of formula 3 such as esters of alanine, cysteine, aspartic acid, glutamic acid, phenylalanine, histidine, and lysine are commercially available. Others can be prepared by methods well known in the art. Some such methods are described in PCT Applications Publication Nos. WO 00/55144, WO 01/19816, WO 02/20485, WO 03/029200, U.S. Provisional Application No. 60/422,337, U. S. Patent No. 6,353,017B1, 6,492,662B1, 353,017 B1 and 6,525,036B1, the disclosures of which are incorporated herein by reference in their entirety.

Hydrolysis of the ester group in 4, followed by reaction of the resulting acid with an amine of formula 5 where E is as defined in the Summary of the Invention provides a compound of Formula (Ia). The reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), O-(7-azabenzotriazol-1-yl)-1,1,3,3, tetra-methyluronium-hexafluorophosphate (HATU), O-benzotriazol-1-yl- N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOAt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) and non-nucleophilic base (e.g., triethylamine, N-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 h to complete. Suitable reaction solvents include, but are not limited to, dimethylformamide, methylene chloride, and the like.

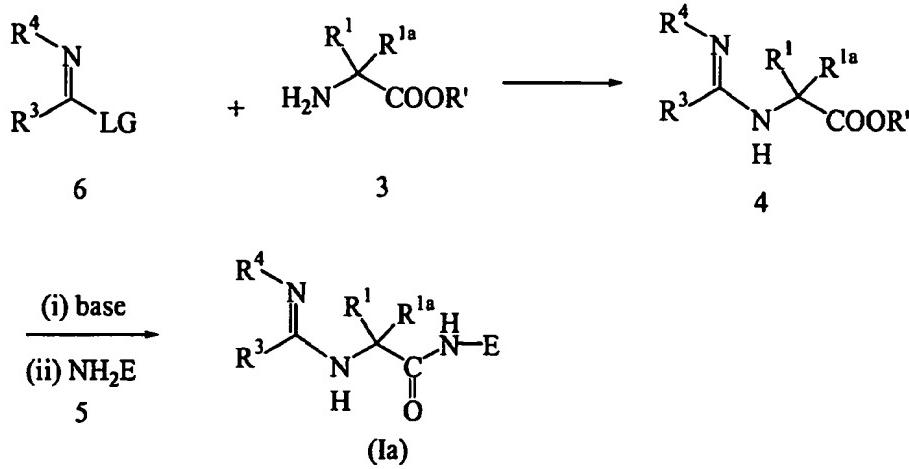
Alternatively, the free acid of compound 4 can be converted to an acid halide and then reacted with 5 to give a compound of Formula (Ia). The reacting is carried out in the presence of a base such as triethylamine, pyridine, and the like and in a suitable organic solvent such as tetrahydrofuran, dioxane, and the like. Compounds of formula 5 are either commercially available or they can be prepared by methods well known in the art. Some such methods are disclosed in working examples below. Other methods are disclosed in U.S. Patent Application Nos.

60/373,176, 09/525,507, and 10/035,783 the disclosures of which are incorporated herein by reference in their entirety.

A compound of Formula (Ia) can be converted to other compounds of Formula (Ia). For example, a compound of Formula (Ia) where E is $-C(R^5)(R^6)C(R^7)(R^8)R^{10}$ where R⁷ is hydrogen and R⁸ is hydroxy can be converted to other compounds of Formula (Ia) where E is $-C(R^5)(R^6)COR^{10}$ by oxidation of the hydroxy group. The oxidation reaction is carried out with an oxidizing agent (e.g., Dess-Martin Periodinane[®], TEMPO/bleach, or the like) in a suitable solvent (e.g., acetonitrile, dichloromethane, methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 h to complete. Detailed descriptions for the synthesis of a compound of Formula (Ia) by the processes in Reaction Scheme 1 are set forth in the Example 1 below.

Alternatively, a Formula (Ia) where E is $-C(R^5)(R^6)X^1$ or $-C(R^{5a})(R^{6a})CN$ and R¹, R^{1a}, R², R³, R⁴, R⁵, R^{5a}, R⁶ and R^{6a} are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 2 below.

Scheme 2



Reaction of a compound of formula 6 where LG is a leaving group such as halo with an amino compound of formula 3 provides a compound of formula 4. The reaction is carried out by methods well known in the art. Some such methods are described in Dunn. A. D., *Org. Prep. Proceed. Int.*, 1998, 30, 709; Lindstroem, S., et. al., *Heterocycles*, 1994, 38, 529; Katritzky, A. R., et. al., *Synthesis*, 1990, 561; Hontz, A. C., et . al., *Org. Synth.*, 1963, IV, 383; and Stephen, H., *J.*

Chem., Soc., 1957, 490. Compound 4 is then converted to a compound of Formula (Ia) as described above.

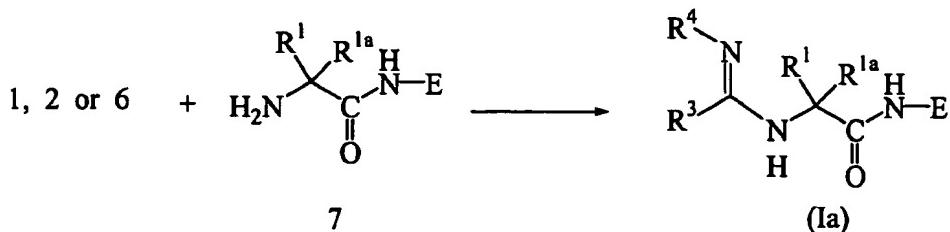
Compounds of formula 6 are either commercially available or they can be readily prepared by methods well known in the art. For example, For example, 3-chloro-1,1-

- 5 dioxobenzo[d]isothiazole is commercially available. 4-Chlorobenzo[e][1,3]oxazin-2-one can be obtained by treating benzo[e][1,3]oxazine-2,4-dione with phosphorus pentachloride in refluxing toluene. Similarly, 3-chloro-2,3-dihydro-thieno[3,4-d]isothiazole 1,1-dioxide and 3-chloro-2,3-dihydrothieno[3,2-d]isothiazole can be prepared from 1,1-dioxide1,1-dioxo-1,2-dihydro-1 λ^6 -thieno[3,4-d]isothiazol-3-one and 1,1-dioxo-1,2-dihydro-1 λ^6 -thieno[3,2-d]isothiazol-3-one
10 respectively, as described above. 1,1-Dioxide1,1-dioxo-1,2-dihydro-1 λ^6 -thieno[3,4-d]isothiazol-3-one and 1,1-dioxo-1,2-dihydro-1 λ^6 -thieno[3,2-d]isothiazol-3-one are described by the procedures described in *J. Org. Chem.*, 1980, 45, 617-620. Other compounds of formula 6 disclosed in preferred embodiment (I) (7) and (8) above, can be prepared from corresponding carbonyl compounds materials known in the art by converting them to the corresponding halo derivative as described above. For examples, the following references describe the synthesis of some of the carbonyl starting materials: *Chem. Ber.* 1962, 84, 509; Cohen, E. Klarberg, B, *JACS*, 1962, 84, 1992-2002; BASF patent, FR 2276309, DE 2430353; Edenhofer, A., Meister, W., *Helv. Chim. Acta*, 1977, 60, 521-523; Kloek, J.A.; Leschinsky, K.L., *J. Org. Chem.*, 1978, 43, 3824-3827; Goya, et al., *J. Heterocycl. Chem.*, 1984, 21, 861-864; Meyer, R.B., and Skibo, E.B., *J. Med. Chem.*, 1979, 22, 944-948; Ochoa, C; and Stud, M., *J. Heterocycl. Chem.*, 1978, 15, 221-224; Edenhofer, A., and Meister, W., *Helv. Chim. Acta*, 1977, 60, 521-523; Goya, et al., *Synthesis*, 1989, 280-282; Monsanto patent, US 4139700; Womhoff, H. and Ertas, M., *Synthesis*, 1985, 190-194; Raffa, *Farmaco Ed. Sci.*, 1957, 12, 41-47; Girare, Y. et al., *J. Chem. Soc. Perkin Trans. 1*, 1979, 1043-1047; Parke, W., *J. Chem. Soc.*, 1950, 1760, 1763; Raffa, *Farmaco Ed. Sci.*, 1960, 15, 25 716-725; Raffa, *Farmaco Ed. Sci.*, 1966, 21, 16-29; Hayman, D. F., et al, *J. Pharm. Pharmacol.*, 1962, 14, 522-533; Raffa, *Farmaco Ed. Sci.*, 1962, 17, 234-243; Blicke, F. F. and Lee, C. M., *J. Org. Chem.*, 1961, 26, 1861-1867; Kotovskaya, S. K., et al., *J. Pharm. Chem.*, 1979, 13, 4, 389-392; Ofiserov, V. I, et al., *Chem. Heterocycl. Compd.*, 1976, 12, 924-927; Thompson, M. E., *Synthesis*, 1988, 9, 733-735; Arranz, M. E., et al., *Heterocycles*, 1977, 45, 9, 1767-1774; Neill, C.
30 G, et al., *Tetrahedron*, 1988, 54, 44, 13645-13654; Phillips, D., et al., *Bioorg. Med. Chem.*, 2002, 10, 5, 1229-1248; Ihara Chem. Ind. Patent FR 231,4185; DE 261,6611, Becke, F. and Hagen, H., *Justus Liebigs Ann. Chem.*, 1969, 729, 146-151; Burri, K. F., *Helv. Chim. Acta.*, 1990, 73, 1, 69-

80; Kwon, Soon-Kyoung and Park, Myung-Sook, *Arzneim. Forsch.*, 1996, 46, 10, 966-971; Lombardino, J. G., *J. Org. Chem.*, 1971, 36, 1843-1845; Hlasta, D. J., et al., *Tet. Lett.*, 1991, 32, 49, 7179-7182; Haworth, L., *J. Chem. Soc.*, 1924, 125, 1304; Moulton, *J. Am. Chem.*, 1891, 13, 200; Zincke, G., *Justus Liebigs Ann. Chem.*, 1922, 427, 249; Remsen, B., *J. Am. Chem.*, 2, 5 1880/1881, 411; Schoop, *Chem. Ber.*, 1881, 14, 223; Weber, *Chem. Ber.*, 1892, 25, 1740; Szabo, *Bull. Soc. Chim. Fr.*, 1953, 771-773; Love, K., *J. Org. Chem.*, 1962, 27, 2177-2180; Jacobsen, *Justus Liebigs Ann. Chem.*, 1881, 206, 175; Finzi, C., *Gazz. Chim. Ital.*, 1938, 68, 132-139; Fahlberg, *Chem. Ber.*, 1887, 20, 1603; de Stevens et al., *J. Med. Pharm. Chem.*, 1959, 1, 565-573; Thomae, K., DE 2749640; Hamor, G. H., *J. Am. Pharm. Assoc. Sci. Ed.* 1960, 49, 280-283; 10 Warren, A. and Hamor, G. H., *J. Pharm. Sci.*, 1961, 50, 625-626; Unterhalt, B. and Moghaddam, S., *Pharmazie*, 1994, 49, 2/3, 115-117; Vega, S., et al., *Dur. J. Med. Chem. Chim. Ther.*, 1988, 23, 329-334; Rohm-Hass Co., U.S. Patent 3562283; Lewis, S. N., *J. Heterocycl. Chem.*, 1971, 8, 591-595; Gilbert, E. E., *J. Org. Chem.*, 1970, 35, 850-852; Shkulev, V. A. et al., *J. Pharm. Chem.*, 1977, 11, 10, 1376-1379; Horii, Patent JP 1683, 1962; Lewis, S. N., *J. Heterocycl. Chem.*, 1971, 8, 591-595; Chekhuta, V. G. et al., *J. Org. Chem. USSR*, 1967, 3, 1763-1766; Schulze, B. and Muehlstaedt, M., *A. Chem. GE*, 1988, 28, 10, 362; Alo, B., et al., *J. Heterocycl. Chem.*, 1992, 29, 1, 61-64; Waldner, A., *Helv. Chim. Acta. GE*, 1989, 72, 1435-1443; Burri, K. F., *Helv. Chim. Acta.*, 1989, 72, 1416-1427; and Zawisza, T. and Malinka, W., *Farmaco Ed. Sci.*, 1986, 41, 9, 676-683.

20 Alternatively, a compound of Formula (Ia) where E is $-C(R^5)(R^6)X^1$ or $-C(R^{5a})(R^{6a})CN$ and $R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6$ and R^{6a} are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 3 below.

Scheme 3

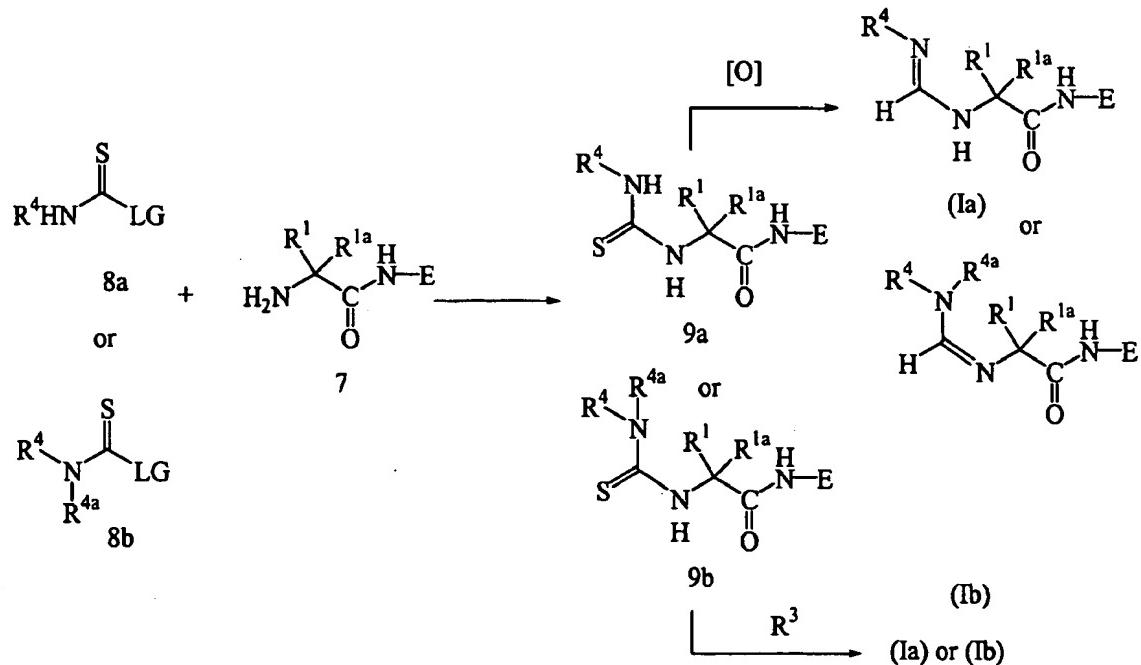


25 Reaction of a compound of formula 1, 2 or 6 with an amino compound of formula 7 provides a compound of Formula (Ia). The reaction is carried out under the reaction conditions described in Scheme 1 above. Compounds of formula 7 can be prepared by reacting an N-

protected amino acid of formula 3 ($R' = H$) with a compound of formula 5 under the coupling reaction conditions described above, followed by removal of the amino protecting group. Suitable amino protecting groups include, but are not limited to, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like. Other methods that can be utilized for preparing compounds of Formula (Ia) and (Ib) 5 are described in PCT Application Publication Nos. WO 02/20485 and WO 03/029200, and U.S. Patent 6,420,364, the disclosures of which are incorporated herein by reference in their entirety.

Alternatively, a compound of Formula (Ia)/(Ib) where E is $-\text{C}(\text{R}^5)(\text{R}^6)\text{X}^1$, R^3 is hydrogen or an amino containing group and is bonded to the carbon via the nitrogen atom, and R^1 , R^{1a} , R^4 , 10 R^5 , and R^6 are as defined in the Summary of the Invention can be prepared by proceeding as in the following Reaction Scheme 4 below.

Scheme 4



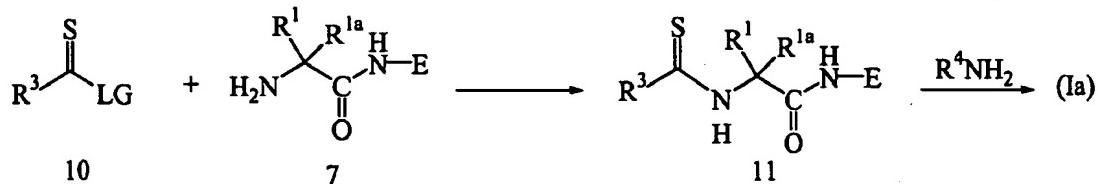
15 Reaction of a compound of formula 8a or 8b where LG is a suitable leaving group such as imidazol-1-yl with an acid addition salt or free base of a compound of formula 7 provides a compound of formula 9a or 9b respectively. The reaction is carried out in the presence of a base such as diisopropylamine, triethylamine, and the like (if acid addition salt of 7 is used) and in a suitable organic solvent such as methylene chloride, dioxane, and the like. Compounds of formula 20 8a and 8b can be readily prepared by reacting an amine of formula R^4NH_2 and $\text{R}^4\text{R}^{4a}\text{NH}$ respectively, with thio coupling agent such as 1,1'-thiocarbonyldiimidazole, and the like.

Compound 9a or 9b is then converted to a compound of Formula (Ia) or (Ib) by reacting it with an R³ group containing a reactive nitrogen atom. For example, a compound of Formula (Ia) where R³ is morpholin-1-yl, piperidin-1-yl, or piperazin-1-yl can be prepared by heating a compound formula 9a with morpholine, piperidine, or piperazine respectively, in the presence of 5 copper sulfate on silica gel and a suitable base such as triethylamine, and the like, in a microwave reactor. Suitable reaction solvents include tetrahydrofuran, and the like. Compound 9a or 9b is then converted to a compound of Formula (Ia) or (Ib) by reacting it with a basic nitrogen containing R³ group such as morpholine, piperidine, and the like.

Alternatively, 9a or 9b can be reacted with an oxidizing agent such as hydrogen peroxide 10 to give a compound of Formula (Ia) or (Ib) where R³ is hydrogen.

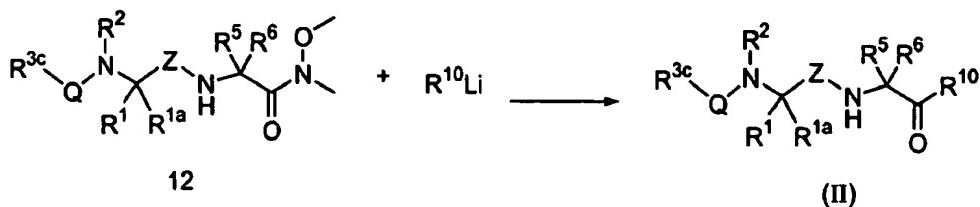
Alternatively, a compound of Formula (Ia) where E is -C(R⁵)(R⁶)X¹, R³ is an amino containing group and is bonded to the carbon via the nitrogen atom and R¹, R^{1a}, R⁴, R⁵, and R⁶ are as defined in the Summary of the Invention can be prepared by proceeding as in the following 15 Reaction Scheme 5 below.

Scheme 5



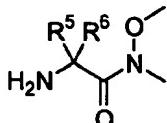
Reaction of a compound of formula 10 where R³ is an amino containing group and is 20 bonded to the carbon via the nitrogen atom with 7 under the presence of a suitable coupling agent such as 2-chloro-1-methylpyridinium iodide provides a compound of formula 11 in which is then reacted with an amine of formula R⁴NH₂ where R⁴ is as defined in the Summary of the Invention to provide a compound of Formula (Ia). Compound 10 is prepared as described in Scheme 4 above e.g., reacting morpholine with 1,1'-thiocarbonyldiimidazole.

Compounds of Formula (II) where Q, R^{3c}, R¹, R^{1a}, R², and Z is as defined in the Summary of the Invention and E is -C(R⁵)(R⁶)(R⁷)(R⁸)R¹⁰ where R⁷ and R⁸ together form oxo can be prepared by proceeding as illustrated and described in Scheme 6 below.



Compounds of Formula (II) in which R⁷ and R⁸ together form oxo can be prepared by reacting an organometallic compound of formula R¹⁰Li with a compound of formula 12. The reaction is carried out in a suitable solvent (e.g. tetrahydrofuran (THF), ether, or the like) at -80 to -70° C, preferably at about -78° C, and requires 30 minutes to an hour to complete. The organometallic compound of formula R¹⁰Li is generated by treating a corresponding organo compound or a brominated derivative thereof, with *n*-butyllithium or *tert*-butyllithium in a suitable solvent (e.g. THF, ether, or the like) at -80 to -70° C, preferably at about -78° C, for approximately 30 minutes to an hour.

Compounds of formula 12 where Z is --CO- can be prepared by reacting an amino acid of formula 13:



15 with a compound of the formula $R^{3c}QN(R^2)C(R^1)(R^{1a})C(O)Y$ where Q and R_{3c} are as defined in the Summary of the invention and Y is hydroxy or an activating group (succinimide, or the like). When Y is an activating group, the reaction is carried out in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, or the like) and in a suitable solvent (e.g. acetonitrile, 20 N,N-dimethylformamide (DMF), dichloromethane, or any suitable combination thereof, or the like) at 10 to 30°C, preferably at about 25°C, and requires 24 to 30 hours to complete. When Y is hydrogen a suitable coupling agent (e.g. benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 25 O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and a base (e.g. N,N-diisopropylethylamine, triethylamine, or the like) is required and the reaction takes about 2 to 3 hours to complete.

Compounds formula 13 can be prepared by reacting a corresponding N-protected alpha amino with *N,O*-dimethylhydroxylamine hydrochloride followed by deprotection of the amino

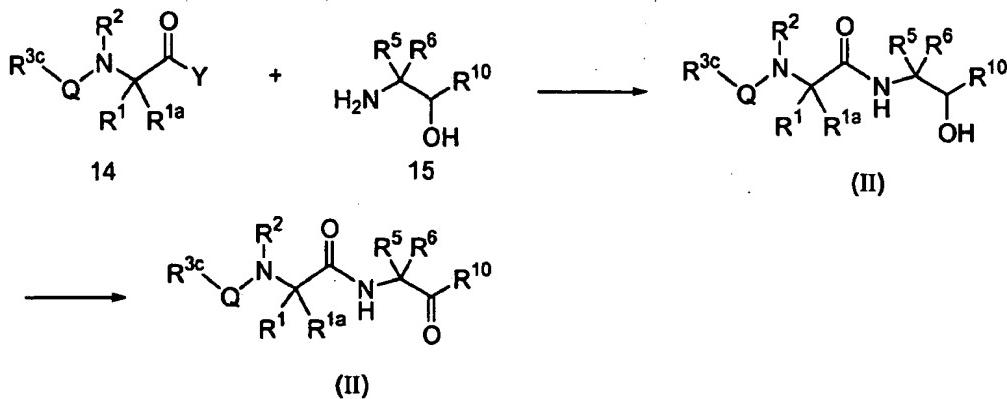
group. The reaction with the *N,O*-dimethylhydroxylamine is carried out in the presence of a suitable coupling agent (PyBOP®, EDC, HBTU, DCC, and the like) and a base (e.g. *N,N*-diisopropylethylamine, triethylamine, or the like) in a suitable solvent (e.g. dichloromethane, DMF, and the like) at 20 to 30° C, preferably at about 25° C, and takes about 2 to 4 hours to complete. Deprotection of the amino group provides the desired compound 13.

Compounds of formula $R^{3c}QN(R^2)C(R^1)(R^{1a})C(O)Y$ can be prepared by reacting a carboxy protected amino acid of formula $NH_2(R^2)C(R^1)(R^{1a})C(O)OPG$ where PG is a suitable protecting group with an acylating agent, a sulfonylating agent, a carbamoyl halide, sulfamoyl halide of formula $R^{3c}COL$, $R^{3c}SO_2L$, $R^{3c}NHCOL$, or $R^{3c}NSO_2L$ respectively. Removal of the carboxy protecting group provides $R^{3c}QN(R^2)C(R^1)(R^{1a})C(O)OH$ which is then reacted with compound 13.

Alternately, compounds of Formula (II) where E is $-C(R^5)(R^6)C(R^7)(R^8)R^{10}$ and other groups are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 7 below:

15

Scheme 7



Reaction of a compound of formula 14 where Y is hydroxy or an activating group (e.g. 2,5-dioxopyrrolidin-1-yl, succinimide, or the like) with a compound of formula 15 under the reaction conditions described in Scheme 6 above provides a compound of Formula (II).

Compounds of formula 15 can be prepared under deprotonation reaction conditions by treating benzoxazole, oxazolo[4,5-*b*]pyridine, 2-pyridin-3-yloxadiazole, 2-pyridin-4-yl-oxadiazole, 2-phenyloxadiazole, and the like, with a Grignard reagent such as isopropylmagnesium chloride and then reacting the resulting organomagnesium reagent with an

alpha-(*N*-protected amino)aldehyde of formula CR⁵R⁶(NHPG)CHO, where PG is a suitable amino protecting group (such as *tert*-butoxycarbonyl, benzyloxycarbonyl, or benzyl) to provide an *N*-protected compound of formula 13 after treatment with an aqueous acid or buffer. Removal of the amino protecting group then provides a compound of formula 15.

5 The addition reaction is typically carried out in an ethereal organic solvent such as tetrahydrofuran, diethyl ether, dioxane, and the like, preferably tetrahydrofuran, at a temperature from about -78 °C to about 40 °C. Preferably, the reaction is carried out from about -10 °C to about 40 °C, more preferably from about -10 °C to about 10 °C. The reaction typically requires an hour to complete. The nucleophilic addition reaction is typically carried out from about -10 °C to 10 about room temperature. Compounds of formula CR⁵R⁶(NHPG)CHO are prepared from commercially available starting materials by methods well known in the art.

The reaction conditions employed for removal of the amino protecting group depends on the nature of the protecting group. For example, if the protecting group is *tert*-butoxycarbonyl, it is removed under acid reaction conditions. Suitable acids are trifluoroacetic acid (TFA), 15 hydrochloric acid, and the like. If the protecting group is benzyl or benzyloxycarbonyl, it is removed under catalytic hydrogenation reaction conditions. Suitable catalyst are palladium, platinum, rhodium based catalysts and others known in the art. Other suitable reaction conditions for their removal can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999. The reaction is carried out in an inert organic 20 solvent methylene chloride, tetrahydrofuran, dioxane, dimethylformamide, and the like.

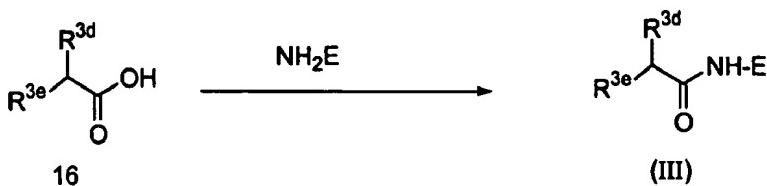
Oxidation of hydroxy group in (II) where R⁷ is hydroxy and R⁸ is hydrogen with a suitable oxidizing agent such as Dess-Martin Periodinane in a halogenated organic solvent such as methylene chloride, chloroform, carbon tetrachloride, and the like, or a mixture of TEMPO/bleach then provides a corresponding compound of Formula (II) where R⁷ and R⁸ together form oxo.

25 The above procedure can be used to prepare compounds of Formula (II) where E is – C(R^{5a})(R^{6a})CN by substituting compound 15 with NH₂C(R^{5a})(R^{6a})CN.

Other methods for preparing compounds of Formula (II) are described in US Patents 6,576,630 and PCT application publication No. WO 00/55126 the disclosures of which are incorporated herein by reference in their entirety.

30 Compounds of Formula (III) where R^{3d}, R^{3e}, and E are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 8 below:

Scheme 8

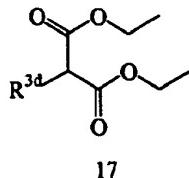


5

Compounds of Formula (III) can be prepared by condensing an acid of formula 16 with an amino compound of formula NH_2E where E is as defined in the Summary of the Invention under conditions described in Scheme 6 above.

Compounds of formula 16 can be prepared by reacting a compound of formula 17:

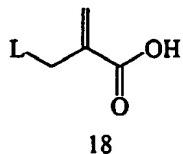
10



17

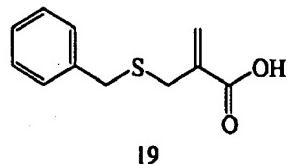
with R^{3c}L in which L is a leaving group and R^{3d} and R^{3e} are as defined in the Summary of the Invention. The reaction involves coupling (or alkylation) followed by alkaline hydrolysis at a temperature during which the dicarboxylic acid formed undergoes mono-decarboxylation. The 15 coupling reaction can be carried out in the presence of a suitable base (e.g. triethylamine) in a suitable solvent (e.g. ethanol). The decarbalkoxylation can be effected under strongly basic conditions (e.g. in the presence of 1N aqueous sodium hydroxide) in a suitable solvent (e.g. ethanol). Detailed descriptions for the synthesis of compounds of Formula 2 by the process described is described in WO 02/051983.

20 Compounds of formula 17, in which R^{3d} and R^{3e} are benzylsulfonylmethyl, can be prepared by reacting a compound of formula 18:



18

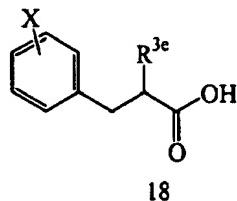
in which L is a halo group, with benzyl mercaptan under strongly basic conditions to produce a compound of formula 19:



5

followed by reaction with benzyl mercaptan in the presence of a suitable coupling reagent (e.g. DMAP) and in a suitable solvent (e.g. DMF). A detailed description of the synthesis of a compound of formula 16 by a similar process as that described above is set forth WO 02/051983.

Compounds of formula 16, in which R^{3d} is biaryl, can be prepared by coupling a compound
10 of formula 18:

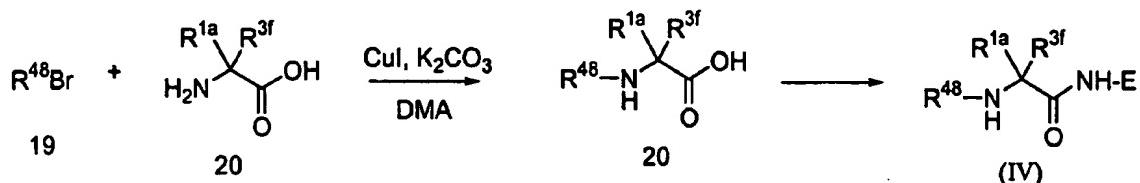


in which X is a halo group and R^{3e} is as defined in the Summary of the Invention, with a compound of ArL, in which Ar is an aryl group and L is a leaving group, to produce a compound
15 of formula 18 in which R^{3d} is biaryl. The coupling reaction takes place in the presence of a suitable catalyst (e.g. tetrakis-triphenylphosphine palladium). A detailed description of the synthesis of a compound of formula 18 by a similar process as that described above is set forth WO 02/051983.

20 Compounds of Formula (IV) where R^{3g} is -NHR⁴⁸ and R^{3f} and E are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 9 below:

Scheme 9

25



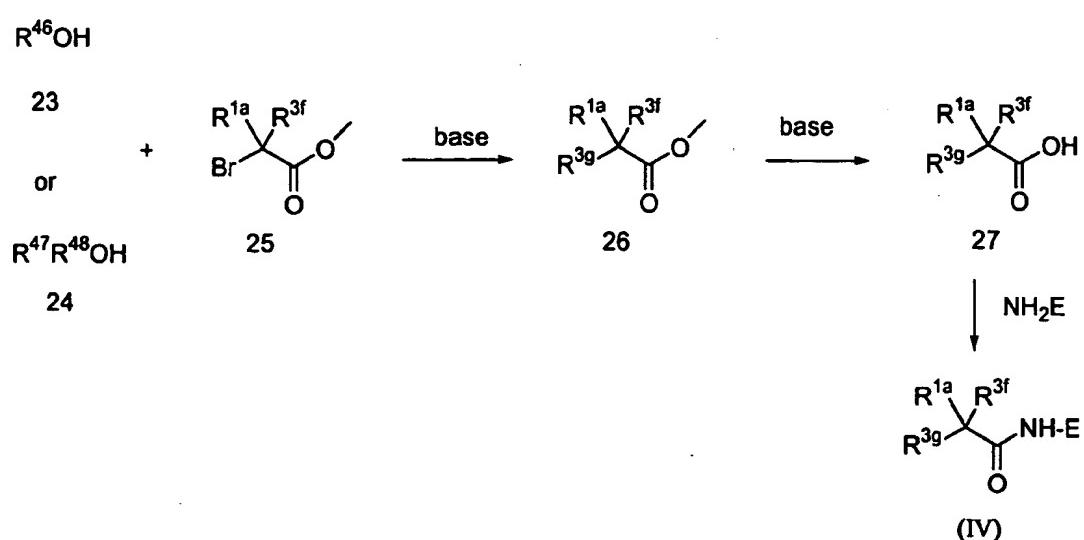
Treatment of a compound of formula 19 with alpha-aminoacetic acid of formula 20 in the presence of copper iodide and a base such as potassium carbonate provides a compound of formula 21. The reaction is carried out in a suitable organic solvent such as dimethylacetamide, and the like.

Compounds of formula 19 and 20 are commercially available or they can be prepared by methods well known in the art.

Treatment of 21 with an amino compound of formula NH_2E where E is as defined in the Summary of the Invention provides a compound of Formula (IV). The reaction is carried out in the presence of a coupling agent under the reaction conditions as described above.

Alternatively, a compound of Formula (IV) where R^{3g} is -OR⁴⁶ or -NR⁴⁷R⁴⁸ can be prepared as illustrated and described in Scheme 10 below.

Scheme 10



Treatment of a compound of formula 23 or 24 where R⁴⁶, R⁴⁷ and R⁴⁸ are as defined in the Summary of the Invention with 2-bromoacetate of formula 25 provides a compound of formula 26
 20 where R^{3g} is -OR⁴⁶ or -NR⁴⁷R⁴⁸ respectively. The reaction is carried out in the presence of a

strong non-nucleophilic base such as sodium hydride, *tert*-butoxide, and the like and in a suitable organic solvent such as dimethylformamide, tetrahydrofuran, and the like. Hydrolysis of the ester group in 26 under basic hydrolysis reaction conditions provides a compound of formula 27. Suitable bases are aqueous lithium hydroxide, sodium hydroxide, and the like. Suitable solvents 5 are alcoholic solvents such as methanol, ethanol, and the like. A compound of formula 27 can then be converted to a corresponding compound of Formula (IV) as described above.

Alternate methods for preparing compounds of Formula (IV) are disclosed in WO 02/098850, the disclosure of which is incorporated herein by reference in its entirety.

10 Additional Processes for Preparing Compounds of Formulae (I)-(IV):

A compound of the present invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the present invention can be prepared by reacting the free acid form of the 15 compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of the present invention are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of the present invention can be prepared using salts of the starting materials or intermediates.

20 The free acid or free base forms of the compounds of the present invention can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of the present invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the present invention in a base addition salt form can be converted to the 25 corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of the compounds of the present invention can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of the present invention with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic 30 acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of the present invention can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of the present invention in unoxidized form can be prepared from *N*-oxides of compounds of the present invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 °C.

Prodrug derivatives of the compounds of the present invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the present invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the present invention can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the present invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of the present invention, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean

Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Preparation of Biological Agents

5 In practicing this invention several processes for the generation or purification of biological agents are used. Methods for preparing the biologics are well known in the art as discussed below.

Monoclonal antibodies are prepared using standard techniques, well known in the art, such as by the method of Kohler and Milstein, *Nature* (1975) 256:495, or a modification thereof, such 10 as described by Buck et al. (1982) *In Vitro* 18:377. Typically, a mouse or rat is immunized with the MenB PS derivative conjugated to a protein carrier, boosted and the spleen (and optionally several large lymph nodes) removed and dissociated into single cells. If desired, the spleen cells may be screened (after removal of non-specifically adherent cells) by applying a cell suspension to a plate or well coated with the antigen. B-cells, expressing membrane-bound immunoglobulin 15 specific for the antigen, will bind to the plate, and will not be rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas. Representative murine myeloma lines for use in the hybridizations include those available from the American Type Culture Collection (ATCC).

Chimeric antibodies composed of human and non-human amino acid sequences may be 20 formed from the mouse monoclonal antibody molecules to reduce their immunogenicity in humans (Winter et al. (1991) *Nature* 349:293; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220; Shaw et al. (1987) *J Immunol.* 138:4534; and Brown et al. (1987) *Cancer Res.* 47:3577; Riechmann et al. (1988) *Nature* 332:323; Verhoeven et al. (1988) *Science* 239:1534; and Jones et al. (1986) *Nature* 321:522; EP Publication No. 519,596, published Dec. 23, 1992; and U.K. Patent 25 Publication No. GB 2,276,169, published Sep. 21, 1994).

Antibody molecule fragments, e.g., F(ab').sub.2, FV, and sFv molecules, that are capable of exhibiting immunological binding properties of the parent monoclonal antibody molecule can be produced using known techniques. Inbar et al. (1972) *Proc. Nat. Acad. Sci. USA* 69:2659; Hochman et al. (1976) *Biochem* 15:2706; Ehrlich et al. (1980) *Biochem* 19:4091; Huston et al. 30 (1988) *Proc. Nat. Acad. Sci. USA* 85(16):5879; and U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

In the alternative, a phage-display system can be used to expand the monoclonal antibody molecule populations in vitro. Saiki, et al. (1986) Nature 324:163; Scharf et al. (1986) Science 233:1076; U.S. Pat. Nos. 4,683,195 and 4,683,202; Yang et al. (1995) J Mol Biol 254:392; Barbas, III et al. (1995) Methods: Comp. Meth Enzymol 8:94; Barbas, III et al. (1991) Proc Natl Acad Sci USA 88:7978.

The coding sequences for the heavy and light chain portions of the Fab molecules selected from the phage display library can be isolated or synthesized, and cloned into any suitable vector or replicon for expression. Any suitable expression system can be used, including, for example, bacterial, yeast, insect, amphibian and mammalian systems. Expression systems in bacteria include those described in Chang et al. (1978) Nature 275:615, Goeddel et al. (1979) Nature 281:544, Goeddel et al. (1980) Nucleic Acids Res. 8:4057, European Application No. EP 36,776, U.S. Pat. No. 4,551,433, deBoer et al. (1983) Proc. Natl. Acad. Sci. USA 80:21-25, and Siebenlist et al. (1980) Cell 20:269.

Expression systems in yeast include those described in Hinnen et al. (1978) Proc. Natl. Acad. Sci. USA 75:1929, Ito et al. (1983) J. Bacteriol. 153:163, Kurtz et al. (1986) Mol. Cell. Biol. 6:142, Kunze et al. (1985) J. Basic Microbiol. 25:141, Gleeson et al. (1986) J. Gen. Microbiol. 132:3459, Roggenkamp et al. (1986) Mol. Gen. Genet. 202:302, Das et al. (1984) J. Bacteriol. 158:1165, De Louvencourt et al. (1983) J. Bacteriol. 154:737, Van den Berg et al. (1990) Bio/Technology 8:135, Kunze et al. (1985) J. Basic Microbiol. 25:141, Cregg et al. (1985) Mol. Cell. Biol. 5:3376, U.S. Pat. Nos. 4,837,148 and 4,929,555, Beach et al. (1981) Nature 300:706, Davidow et al. (1985) Curr. Genet. 10:380, Gaillardin et al. (1985) Curr. Genet. 10:49, Ballance et al. (1983) Biochem. Biophys. Res. Commun. 112:284-289, Tilburn et al. (1983) Gene 26:205-221, Yelton et al. (1984) Proc. Natl. Acad. Sci. USA 81:1470-1474, Kelly et al. (1985) EMBO J. 4:475479; European Application No. EP 244,234, and International Publication No. WO 91/00357.

Expression of heterologous genes in insects can be accomplished as described in U.S. Pat. No. 4,745,051, European Application Nos. EP 127,839 and EP 155,476, Vlak et al. (1988) J. Gen. Virol. 69:765-776, Miller et al. (1988) Ann. Rev. Microbiol. 42:177, Carbonell et al. (1988) Gene 73:409, Maeda et al. (1985) Nature 315:592-594, Lebacq-Verheyden et al. (1988) Mol. Cell. Biol. 8:3129, Smith et al. (1985) Proc. Natl. Acad. Sci. USA 82:8404, Miyajima et al. (1987) Gene 58:273, and Martin et al. (1988) DNA 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow et al. (1988)

Bio/Technology 6:47-55, Miller et al. (1986) GENERIC ENGINEERING, Setlow, J. K. et al. eds., Vol. 8, Plenum Publishing, pp. 277-279, and Maeda et al. (1985) Nature 315:592-594.

Mammalian expression can be accomplished as described in Dijkema et al. (1985) EMBO J. 4:761, Gorman et al. (1982) Proc. Natl. Acad. Sci. USA 79:6777, Boshart et al. (1985) Cell 5 41:521, and U.S. Pat. No. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham et al. (1979) Meth. Enz. 58:44, Barnes et al. (1980) Anal. Biochem. 102:255, U.S. Pat. Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655 and Reissued U.S. Pat. No. RE 30,985, and in International Publication Nos. WO 90/103430, WO 87/00195.

The production of recombinant adenoviral vectors are described in U.S. Pat. No. 10 6,485,958.

Botulinum toxin type A can be obtained by establishing and growing cultures of *Clostridium botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known procedures.

Any of the above-described protein production methods can be used to provide the 15 biologic that would benefit from the present invention.

Testing

The cysteine protease inhibitory activity, in particular, the Cathepsin S inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill 20 in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease-induced hydrolysis of a peptide-based substrate. Details of assays for measuring protease inhibitory activity are set forth in Biological Examples 1-5, *infra*.

25 Administration and Pharmaceutical Compositions

In general, a compound of the present invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the 30 potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of compounds of the present invention may range from about 10 micrograms per kilogram body weight ($\mu\text{g}/\text{kg}$) per day to about 20 milligram per kilogram body weight (mg/kg)

per day, typically from about 100 µg/kg/day to about 10 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 1 mg/day to about 1.6 g/day, typically from about 1 mg/day to about 100 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to 5 ascertain a therapeutically effective amount of a compound of the present invention for treating a given disease.

The compounds of the present invention can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can 10 take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of the present invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be 15 any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients 20 may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of the present invention in the composition may vary widely 25 depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of the present invention for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form 30 for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of the present invention are described in Example 1 below.

Examples

Biological Examples

Example 1

Cathepsin B Assay

5 Solutions of test compounds in varying concentrations were prepared in 10 µL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 µL, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylene sorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 µL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds
10 on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 nMoles in 25 µL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

15 Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

Example 2

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 µL of dimethyl
20 sulfoxide (DMSO) and then diluted into assay buffer (40 µL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 µL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 µL of assay buffer) was added to the assay solutions and hydrolysis was followed
25 spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

30

Example 3

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate,

5 covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to

10 exhibit cathepsin L inhibitory activity.

Example 4

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); β -mercaptoethanol, 2.5 mM; and BSA, 0.00%. Human cathepsin S (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Val-Val-Arg-AMC (4 nMoles in 25 μ L of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity.

25

Example 5

Cathepsin F Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); DTT, 2.5 mM; and BSA, 0.01%. Human cathepsin F (0.1 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for

5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (2 nMoles in 25 µL of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using
5 standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin F inhibitory activity.

Example 6

10 In vitro Lip10 accumulation assay

During normal antigen presentation, Lip10 is proteolytically degraded to enable loading of a peptide fragment and subsequent MHC-II presentation on the surface of antigen presenting cells. The cleavage process is mediated by Cathepsin S. Thus, the Lip10 assay is an *in vitro* measure of a
15 compound's ability to block cathepsin S and by extension antigen presentation. A compound that causes the accumulation of Lip10 at low concentration would be expected to block presentation of antigens.

Method:

Raji cells (4×10^6) were cultured with 0.02% DMSO or different concentrations of
20 Cathepsin S inhibitors in RPMI medium 1640 containing 10 % (v/v) FBS, 10 mM HEPES, 2 mM L-glutamine, and 1 mM sodium pyruvate for four hours at 37°C in 5% CO₂ humidified atmosphere. After the culture period, cells were washed with cold PBS and cells were then lysed in NP-40 lysis buffer (5 mM EDTA, 1% NP-40, 150 mM NaCl, and 50 mM Tris, pH 7.6) with protease inhibitors. Protein determinations were performed and lysate samples were boiled in
25 reducing SDS sample buffer. Proteins were separated by electrophoresis on 12% NuPAGE® Bis-Tris gels. Proteins were then transferred to nitrocellulose membranes, and after incubation with blocking buffer (5% non-fat dry milk in PBS-Tween), the blots were incubated with the primary antibody against human CD74 invariant chain synthetic peptide (1.5 to 2 µg/ml of mouse anti-CD74 monoclonal antibody, PIN.1, Stressgen Biotechnologies). Blots were then incubated with
30 the secondary antibody, horseradish peroxidase conjugated donkey anti-mouse IgG, at a 1:10,000 dilution. Immunoreactive proteins were detected by chemiluminescence reaction using Pierce Super Signal® West Pico chemiluminescence substrate.

Pharmaceutical Composition Examples

5 The following are representative pharmaceutical formulations containing a compound of the present invention.

Tablet Formulation

10 The following ingredients are mixed intimately and pressed into single scored tablets.

	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule Formulation

20 The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

30 The following ingredients are mixed to form a suspension for oral administration.

	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
35 propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
40 colorings	0.5 mg
distilled water	q.s. to 100 mL

Injectable Formulation

45 The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g

sodium acetate buffer solution, HCl (1 N) or NaOH (1 N) water (distilled, sterile)	0.4 M 2.0 mL q.s. to suitable pH q.s. to 20 mL
--	--

5 All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

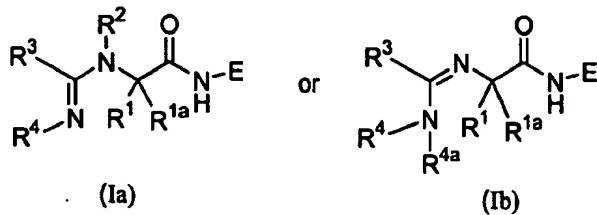
10 A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

15 The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is Claimed:

1. A method of treating a patient undergoing treatment with a biologic wherein the biologic causes a deleterious immune response in the patient comprising administering to the patient a Cathepsin S inhibitor.
- 5 2. The method of Claim 1 wherein the patient is in need of such treatment.
3. The method of Claim 1 or 2 wherein the biologic is Remicade®, Refacto®, Referon-A®, Factor VIII, Factor VII, Betaseron®, Epopen®, Embrel®, Interferon beta, Botox®, Fabrazyme®, Elspar®, Cerezyme®, Myobloc®, Aldurazyme®, Verluma®, Interferon alpha, Humira®, Aranesp®, Zevalin® or OKT3.
- 10 4. A method of treating immune response in an animal caused by administration of a biologic to the animal which method comprises administering to the animal in need of such treatment a therapeutically effective amount of a Cathepsin S inhibitor.
5. A method of conducting a clinical trial for a biologic comprising administering to an individual participating in the clinical trial a Cathepsin S inhibitor with the biologic.
- 15 6. A method of prophylactically treating immunological reponse in a person undergoing treatment with a biologic wherein the immunological response is caused by the biologic said method comprising administering the person a Cathepsin S inhibitor.
7. A method of determining the loss of efficacy of a biologic in an animal due to the immune response caused by the biologic in the animal comprising administering the biologic to the animal in the presence and absence of a Cathepsin S inhibitor.
- 20 8. A method of improving the efficacy of a biologic in an animal comprising administering the biologic to the animal with a Cathepsin S inhibitor.
9. The method of any of the Claims 1-8 wherein the Cathepsin S inhibitor is administered prior to the administration of the biologic.
- 25 10. The method of any of the Claims 1-8 wherein the Cathepsin S inhibitor is administered concomitantly with the biologic.
11. The method of any of the Claims 1-8 wherein the Cathepsin S inhibitor is administered after the administration of the biologic.
12. The method of any of the Claims 1-8 wherein the Cathepsin S inhibitor is:
- 30 (a) a compound of Formula (Ia) or (Ib):



wherein:

E is:

- 5 (i) $-C(R^5)(R^6)X^1$ where X^1 is $-CHO$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$,
 $-C(R^7)(R^8)R^{10}$, $-C(O)C(O)R^{10}$, $-CH=CHS(O)_2R^{10}$, $-C(R^7)(R^8)C(R^7)(R^8)OR^{10}$, $-C(R^7)(R^8)CH_2OR^{10}$,
 $-C(R^7)(R^8)C(R^7)(R^8)R^{10}$, $-C(R^7)(R^8)CH_2N(R^{11})SO_2R^{10}$, $-C(R^7)(R^8)CF_2C(O)NR^{10}R^{11}$,
 $-C(R^7)(R^8)C(O)NR^{10}R^{11}$, $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2OR^{11}$,
 $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2NR^{10}R^{11}$, or

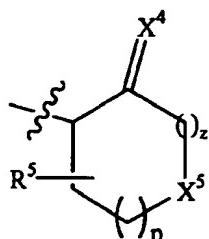
10 where:

R^5 and R^{5a} are independently hydrogen or alkyl; and

R⁶ and R^{6a} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -alkylene-X-R¹² (where X is -O-, -NR¹³-, -S(O)_{n1}-, -CONR¹³-, -NR¹³CO-, -NR¹³C(O)O-, -NR¹³CONR¹³-, -OCONR¹³-, -NR¹³SO₂-, -SO₂NR¹³-, -NR¹³SO₂NR¹³-, -CO-, -OCO-, or -C(O)O- where n1 is 0-2, R¹² hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl) and each R¹³ is hydrogen or alkyl wherein the aromatic or alicyclic ring in R⁶ and R^{6a} is optionally substituted with one, two, or three R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in R^a is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl; or

R⁵ and R⁶ and R^{5a} and R^{6a} taken together with the carbon atom to which both R⁵ and R⁶ and R^{5a} and R^{6a} are attached form (i) cycloalkylene optionally substituted with one or two R^b independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxy carbonyl, or (ii)

- heterocycloalkylene optionally substituted with one to four alkyl or one or two R^c independently selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)_{n2}R¹⁴, -alkylene-S(O)_{n2}-
- 5 R¹⁵, -COOR¹⁶, -alkylene-COOR¹⁷, -CONHR¹⁸R¹⁹, or -alkylene-CONHR²⁰R²¹ (where n2 is 0-2 and R¹⁴-R¹⁷, R¹⁸ and R²⁰ are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and R¹⁹ and R²¹ are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;
- 10 R⁷ is hydrogen or alkyl;
- R⁸ is hydroxy; or
- R⁷ and R⁸ together form oxo;
- 15 R⁹ is hydrogen, halo, alkyl, aralkyl or heteroaralkyl; and
- R¹⁰ is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in R¹⁰ is optionally substituted with one, two, or three R^d independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl,
- 20 aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, aralkyl, heteroaryl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl wherein the aromatic or alicyclic ring in R^d is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino; and
- 25 R¹¹ is hydrogen or alkyl; or
- (iii) a group of formula (a):



(a)

where:

n is 0, 1, or 2;

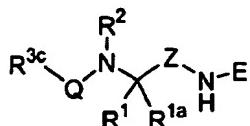
z is 1;

- 5 X⁴ is selected from -NR²²-, -S-, or -O- where R²² is hydrogen, alkyl, or alkoxy; and
X⁵ is -O-, -S-, -SO₂-, or -NR²³- where R²³ is selected from hydrogen, alkyl, haloalkyl,
hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl,
heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, -S(O)₂R²⁴, -alkylene-S(O)_{n3}-R²⁵, -COOR²⁶, -
alkylene-COOR²⁷, -CONR²⁸R²⁹, or -alkylene-CONR³⁰R³¹ (where n3 is 0-2 and R²⁴-R²⁷, R²⁸ and
10 R³⁰ are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,
cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and R²⁹ and R³¹ are
independently hydrogen or alkyl) where the aromatic or alicyclic ring in X⁵ is optionally
substituted with one, two, or three substituents independently selected from alkyl, haloalkyl,
alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl
15 and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl;
- R⁵ is as defined above;
- R¹ is hydrogen or alkyl;
- R^{1a} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl,
heteroaralkyl, heterocycloalkylalkyl, or -alkylene-X²-R³² [wherein X² is -NR³³-, -O-, -S(O)_{n4}-, -
20 CO-, -COO-, -OCO-, -NR³³CO-, -CONR³³-, -NR³³SO₂-, -SO₂NR³³-, -NR³³COO-, -OCONR³³-, -
NR³³CONR³⁴, or -NR³³SO₂NR³⁴- (where R³³ and R³⁴ are independently hydrogen, alkyl, or acyl
and n4 is 0-2) and R³² is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl] wherein said
alkylene chain is optionally substituted with one to six halo and wherein the aromatic or alicyclic
25 ring in R^{1a} is optionally substituted with one, two, or three R⁶ independently selected from alkyl,
haloalkyl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminocarbonyl, aminosulfonyl, acyl,
hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxycarbonyl, aryl,
heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, monosubstituted amino,
disubstituted amino, or acyl; or
- 30 R¹ and R^{1a} together with the carbon atoms to which they are attached form cycloalkylene
or heterocycloalkylene ring wherein said cycloalkylene or heterocycloalkylene is optionally
substituted with one or two R^f independently selected from alkyl, halo, haloalkyl, hydroxyalkyl,

keto, or $\text{-SO}_2\text{R}$ where R is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl where the aromatic or alicyclic ring in R^f is optionally substituted with one, two, or three substitutents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, halo, carboxy, or alkoxycarbonyl;

- 5 R^2 is hydrogen or alkyl;
- R^3 is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, amino, mono or disubstituted amino, or $-\text{alkylene-X}^3\text{-R}^{35}$ [wherein X^3 is $-\text{NR}^{36}\text{-}$, $-\text{O-}$, $-\text{S(O)}_{n5}\text{-}$, $-\text{CO-}$, $-\text{COO-}$, $-\text{OCO-}$, $-\text{NR}^{36}\text{CO-}$, $-\text{CONR}^{36}\text{-}$, $-\text{NR}^{36}\text{SO}_2\text{-}$, $-\text{SO}_2\text{NR}^{36}\text{-}$, $-\text{NR}^{36}\text{COO-}$, $-\text{OCONR}^{36}\text{-}$, $-\text{NR}^{36}\text{CONR}^{37}\text{-}$, or $-\text{NR}^{36}\text{SO}_2\text{NR}^{37}\text{-}$ (where R^{36} and R^{37} are independently hydrogen, alkyl, or acyl and $n5$ is 0-2) and R^{35} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the aromatic or alicyclic rings in R^3 are optionally substituted by one, two, or three R^g independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl,
- 10 R^4 is hydrogen, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, alkylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R^g are optionally substituted with one, two, or three R^h wherein R^h is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, alkylamino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;
- 15 R^4 is hydrogen, alkyl, hydroxy, nitrile, or $-(\text{alkylene})_{n6}\text{-X}^6\text{-R}^{38}$ (where X^6 is $-\text{O-}$, $-\text{NR}^{39}\text{-}$, $-\text{S(O)}_{n7}\text{-}$, $-\text{NR}^{39}\text{CO-}$, $-\text{CO-}$, or $-\text{OC(O)-}$ where $n6$ is 0 or 1, $n7$ is 0-2, and R^{39} is hydrogen or alkyl and R^{38} is hydrogen, alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl, or quinoxalinyl where R^{38} is optionally substituted with one, two, or three R^i independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, monosubstituted amino, disubstituted amino, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, or

- heterocycloalkyl where the aromatic or alicyclic ring in R^j is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl; or
- R³ and R⁴ in (Ia) or (Ib) together with the atoms to which they are attached form heteroaryl or heterocycloalkyl ring optionally fused to an aryl or heteroaryl ring wherein said rings are optionally substituted on the aromatic and/or non-aromatic portion of the rings with one, two, or three R^j;
- each R^j and R^{4a} is independently:
- hydrogen, alkyl optionally interrupted by one or two N, O, C(O), S, S(O), or S(O)₂ and
- 10 optionally substituted by amino, hydroxy, halo, alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranly, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;
- 15 halo, alkoxy, alkylthio, hydroxy, carboxy, aryl, aryloxy, aroyl, heteroaryl, alkanoyl, -C(O)OR where (R is hydrogen, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, aminoalkyl, heterocycloalkyl, or heterocycloalkylalkyl), aminocarbonyl, aminosulfonyl, alkylsulfonyl, aryloxycarbonyl, benzyloxycarbonyl, alkanoylamino, alkylaminocarbonyl, dialkylaminocarbonyl,
- 20 alkoxy carbonylamino, aroylamino, amino, alkylamino, dialkylamino, alkylthio, arylthio, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, cycloalkyl, benzyloxy, or ureido wherein each of the aforementioned groups in R^{4a} and R^j is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, alkyl, alkoxy, haloalkyl, haloalkoxy, oxo, carboxy, nitrile, nitro or NH₂C(O)-; or
- 25 (b) a compound of Formula (II):



(II)

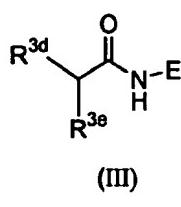
where:

E, R¹, and R^{1a} are as defined above;

Z is -CO- or -CH₂SO₂-; or

Q is -CO-, -SO₂-, -OCO-, -NRCO-, or -NRSO₂- where R is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

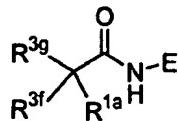
- R^{3c} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X⁸-R⁴⁰ [wherein X⁸ is -NR⁴¹-, -O-, -S(O)_{n8}-, -CO-, -COO-, -OCO-, -NR⁴¹CO-, -CONR⁴¹-, -NR⁴¹SO₂-, -SO₂NR⁴¹-, -NR⁴¹COO-, -OCONR⁴¹-, -NR⁴¹CONR⁴²-, or -NR⁴¹SO₂NR⁴²- (where R⁴¹ and R⁴² are independently hydrogen, alkyl, or acyl and n8 is 0-2) and R⁴⁰ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the alkylene chain in R^{3c} is optionally substituted with one to three halo atoms and the aromatic and alicyclic rings in R^{3c} are optionally substituted by one, two, or three R^k independently selected from alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, aralkylaminosulfonyl, aminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R^k are optionally substituted with one, two, or three R¹ wherein R¹ is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;
- (c) a compound of Formula (III):



- 25 where E is as defined above;

R^{3d} and R^{3e} are independently -alkylene-X⁹-R⁴³ [wherein X⁹ is bond, -NR⁴⁴-, -O-, -S(O)_{n9}-, -CO-, -COO-, -OCO-, -NR⁴⁴CO-, -CONR⁴⁴-, -NR⁴⁴SO₂-, -SO₂NR⁴⁴-, -NR⁴⁴COO-, -OCONR⁴⁴-, -NR⁴⁴CONR⁴⁵-, or -NR⁴⁴SO₂NR⁴⁵- (where R⁴⁴ and R⁴⁵ are independently hydrogen, alkyl, or acyl and n9 is 0-2) and R⁴³ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,

- heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl] wherein the alkylene chain is optionally substituted with one to three halo atoms and the aromatic or alicyclic rings in R^{3d} and R^{3e} are optionally substituted by one, two, or three R^m independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, carboxy,
- 5 alkoxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkylcarbamoyloxy, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, aminocarbonyl, amino, monosubstituted or disubstituted amino and one substituent selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio,
- 10 arylsulfonyl, arylsulfinyl, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, or aralkylaminosulfonyl, wherein the aromatic or alicyclic ring in R^m is optionally substituted with one, two, or three Rⁿ wherein Rⁿ is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, alkylsulfonylamino, arylsulfonylamino,
- 15 heteroarylsulfonylamino, heteroaralkylsulfonylamino, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;
- (d) a compound of Formula (IV):



(IV)

where:

- 20 E, and R^{1a} are as defined above;
- R^{3f} is hydrogen;
- R^{3g} is hydrogen, fluoro, -OR⁴⁶ or -NR⁴⁷R⁴⁸ where:
- R⁴⁶ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -(alkylene)n₁₀-X¹⁰-R⁴⁹ [wherein n₁₀ is 0 or 1, X¹⁰ is -CO- or -CONR⁵⁰- where R⁵⁰ is hydrogen, alkyl, or alkoxyalkyl, and R⁴⁹ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl or R⁴⁹ and R⁵⁰ together with the nitrogen atom to which they are attached from heterocycloalkyl], or -alkylene-X¹¹-R⁵¹ [wherein X¹¹ is -NR⁵²-, -O-, -S(O)_{n11}-, -COO-, -OCO-, -NR⁵²CO-, -NR⁵²SO₂-, -SO₂NR⁵²-, -NR⁵²COO-, -
- 25

- OCONR⁵²-, -NR⁵²CONR⁵³-, or -NR⁵²SO₂NR⁵³- [where n11 is hydrogen or alkyl, R⁵² is hydrogen or alkyl, and R⁵¹ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl or R⁵¹ and R⁵² or R⁵³ together with the nitrogen atom to which they are attached from heterocycloalkyl] wherein the alkylene chain is optionally substituted with one to three halo atoms and the aromatic or alicyclic rings in R⁴⁶ are optionally substituted by one, two, or three R^o independently selected from alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, carboxy, alkoxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkylcarbamoyloxy,
- 5 alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, aminocarbonyl, amino, monosubstituted or disubstituted amino and one radical selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio, arylsulfonyl, arylsulfinyl, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, or aralkylaminosulfonyl wherein the
- 10 aromatic and alicyclic rings in R^o are optionally substituted with one, two, or three R^p wherein R^p is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;
- 15 R⁴⁷ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl; and
- 20 R⁴⁸ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl provided that one of R⁴⁷ and
- 25 R⁴⁸ is other than hydrogen and wherein the aromatic or alicyclic rings in R⁴⁷ and R⁴⁸ are optionally substituted by one, two, or three R^q independently selected from alkyl, halo, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, carboxy, alkoxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkylcarbamoyloxy, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl,
- 30 dialkylaminosulfonyl, amino, monosubstituted or disubstituted amino and one radical selected from aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, aryloxycarbonyl, arylthio, arylsulfonyl, arylsulfinyl,

- aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, or
aralkylaminosulfonyl wherein the aromatic and alicyclic rings are optionally substituted with one,
two, or three R^r wherein R^r is independently selected from alkyl, halo, haloalkyl, haloalkoxy,
hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl,
5 amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido,
or alkoxycarbonyl; or
R^{3f} and R^{3g} are fluoro; or
(f) 7-(2,2-dimethylpropyl)-6-thiophen-2-ylmethyl-7H-pyrrolo-[2,3-d]pyrimidine-2-carbonitrile;
or
10 a pharmaceutically acceptable salts thereof.
13. The method of any of the Claims 1-8 wherein the Cathepsin S inhibitor is selected from:
N-[1*R*-(benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonylethyl]-
morpholine-4-carboxamide;
2*S*-acetylamino-*N*-(2-oxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-
15 cyclohexylpropionamide;
2*S*-acetylamino-*N*-(2-oxazol-2-yl-2-hydroxy-1*S*-phenethyl)-3-cyclohexylpropionamide;
2*S*-acetylamino-*N*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethyl]-3-cyclohexyl-
propionamide;
2*S*-acetylamino-*N*-(5-benzothiazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropion-
20 amide;
N-[1*S*-(1*S*-phenethyl-2-benzooxazol-2-yl-1-oxoethylcarbamoyl)-2-naphth-2-ylethyl]-
piperidine-4-carboxamide;
2*S*-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropion-
amide;
25 *tert*-butyl 1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl-
carbamate;
2*S*-acetylamino-*N*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropyl]-3-cyclohexyl-
propionamide;
30 benzyl 1*S*-(benzooxazol-2-ylcarbonylmethylcarbamoyl)-3-methylbutylcarbamate;
benzyl 1*S*-(5-phenylbenzooxazol-2-ylcarbonylmethylcarbamoyl)-3-methylbutylcarbamate;
2*S*-acetylamino-*N*-(1*S*-oxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropionamide;
2-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-phenylpropionamide;

- benzyl 1*S*-(1*S*-benzoxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-naphthalen-2-yl-ethylcarbamate;
- 2-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl]-3-(2-fluorophenyl)-propionamide;
- 5 2*S*-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-2-methyl-3-phenyl-propionamide;
- tert-butyl 1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-phenylpropyl-carbamate;
- 10 2-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-1,2,3,4-tetrahydroiso-quinoline-3*S*-carboxamide;
- 2*S*-acetylamino-*N*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-(2-chlorophenyl)-propionamide;
- 15 2-acetylamino-*N*-(1-benzoxazol-2-ylcarbonyl-3-phenylpropyl)-3-(2-trifluoromethyl-phenyl)propionamide;
- benzyl 1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methyl-butylcarbamate;
- 20 *N*-{1*S*-[1*S*-(benzoxazol-2-ylcarbonyl)-3-phenylpropylsulfamoylmethyl]-3-methylbutyl}acetamide;
- benzyl 1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methyl-25 butylcarbamate;
- N*-[1-(1-benzoxazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-3-methylbutyl]-acetamide;
- tert-butyl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzylsulfanyl)ethylcarbamate;
- 25 tert-butyl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzyl-sulfanylethylcarbamate;
- N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzyl-sulfanyl)ethyl]isonicotinamide;
- 30 9H-fluoren-9-ylmethyl 1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethylcarbamate;
- tert-butyl 4-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyano-benzylsulfanyl)ethylcarbamoylpiperidine-1-carboxylate;

- benzyl 4-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]-tetrahydropyran-4-carboxamide;
- 5 *N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]-nicotinamide;
- N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfonyl-ethyl]pyrazine-2-carboxamide;
- 4-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 10 *N*-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethyl]-isonicotinamide;
- tert*-butyl 4-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(3-methylpyrid-2-ylmethylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 15 tetrahydropyran-4-yl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzylsulfanylethylcarbamate;
- N*-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethyl]tetrahydropyran-4-carboxamide;
- N*-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexylethyl]-6-
- 20 hydroxynicotinamide;
- tert*-butyl 4-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyano-benzylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- N*-[1*R*-(2-benzoxazol-2-1-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-(2-cyanobenzyl-sulfonyl)ethyl]isonicotinamide;
- 25 *tert*-butyl 1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-benzyl-sulfonylethylcarbamate;
- N*-[1*R*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-pyridin-3-yl-methylsulfonylethyl]pyrazine-2-carboxamide;
- N*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-cyclohexyl-2*S*-(3-pyridin -3-yl-ureido)propionamide;
- N*-[1*S*-(2-benzoxazol-2-yl-2-hydroxy-1*S*-phenethylethylcarbamoyl)-2-cyclohexyl-ethyl]morpholine-4-carboxamide;

- tert*-butyl 4-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 5 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-benzylsulfonylethyl]tetrahydropyran-4-carboxamide;
- 10 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]pyrazine-2-carboxamide;
- 15 *tert*-butyl 4-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- 20 *tert*-butyl 4-[1*S*-(1-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyridin-2-ylmethylsulfonyl)ethylcarbamoyl]piperidine-1-carboxylate;
- 25 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethyl]isonicotinamide;
- 30 tetrahydropyran-4-yl 1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethylcarbamate;
- benzyl 4-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexyl-ethylcarbamoyl]piperidine-1-carboxylate;
- N*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexyl-2*S*-(3-pyridin-3-ylureido)propionamide;
- N*-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-morpholine-4-carboxamide;
- N*-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]isonicotinamide;
- N*-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-tetrahydropyran-4-carboxamide;
- N*-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-6-hydroxynicotinamide;
- N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]morpholine-4-carboxamide;
- N*-[1*R*-(2-benzooxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-benzylsulfonyl-ethyl]morpholine-4-carboxamide;

- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(3,5-dimethylisoxazol-4-yl-methylsulfonyl)ethyl]morpholine-4-carboxamide;
- N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(3,5-dimethylisoxazol-4-yl-methylsulfonylethyl]isonicotinamide;
- 5 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzyl-sulfonyl)ethyl]piperidine-4-carboxamide;
- N-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-piperidine-4-carboxamide hydrochloride;
- 10 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-yl-methylsulfonyl)ethyl]piperidine-4-carboxamide;
- N-(1*S*-benzooxazol-2-ylcarbonylbutyl)-2*R*-methylsulfonylamino-3-benzylsulfonyl-propionamide;
- Methyl 1*R*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2-benzylsulfonylethyl-Carbamate;
- 15 N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- 2*S*-acetylamino-*N*-(2-benzooxazol-2-yl-1*S*-butyl-2-hydroxyethyl)-3-cyclohexylpropionamide;
- 20 2*S*-acetylamino-*N*-(1*S*-benzooxazol-2-ylcarbonylpentyl)-3-cyclohexylpropionamide;
- tert-butyl 1*S*-[1-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]carbamate;
- 2*S*-acetylamino-*N*-(1-benzooxazol-2-ylcarbonyl)-3-phenylpropyl)-3-cyclohexylpropionamide;
- 25 2*S*-acetylamino-*N*-(1-benzooxazol-2-ylcarbonylcyclobutyl)-3-cyclohexylpropionamide;
- 2*S*-acetylamino-*N*-(1*R*-benzooxazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexylpropionamide;
- 2*S*-acetylamino-*N*-(2-benzooxazol-2-yl-2-hydroxy-1*R*-phenylpropyl)-3-cyclohexyl-propionamide;
- 30 N-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethyl]-3H-imidazole-4-carboxamide;
- N-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenylethylethylcarbamoyl)-2-cyclohexyl-ethyl]-3H-imidazole-4-carboxamide;

- tert*-butyl 1*R*-(1-benzooxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfonylethylcarbamate;
- 5 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-o-tolylmethylsulfonylethyl]morpholine-4-carboxamide;
- 10 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 15 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-chlorobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 20 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;
- 25 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 30 *N*-[1*R*-(1*S*-benzooxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-o-tolylmethylsulfonylethyl]morpholine-4-carboxamide;
- 35 *N*-[1*R*-(2-benzooxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-(2-chlorobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 40 *N*-[1*R*-(2-benzooxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 45 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]piperidine-4-carboxamide;
- 50 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl-ethyl]morpholine-4-carboxamide;
- 55 *N*-[1*R*-(1*R*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonyl-ethyl]morpholine-4-carboxamide;
- 60 *N*-[1*R*-(1-benzooxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfonylethyl]-morpholine-4-carboxamide;
- 65 benzyl 1*S*-(2-benzooxazol-2-yl-2-hydroxyethylcarbamoyl)-3-methylbutylcarbamate;

- 2*S*-acetylamino-*N*-(2-benzoxazol-2-yl-1*S*-methyl-2-oxoethyl)-3-cyclohexylpropionamide;
- 5 *tert*-butyl 1*R*-(1-benzoxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-benzylsulfanylethylcarbamate;
- 10 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- 15 *N*-[1-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-3-phenylsulfonylpropyl]-morpholine-4-carboxamide;
- 20 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 25 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethyl]morpholine-4-carboxamide;
- 30 2-[2-(1-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-morpholin-4-ylcarbonylamino)-ethanesulfonylmethyl]pyridine-1-oxide;
- 35 *N*-[3-phenylsulfonyl-1-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)propyl]-morpholine-4-carboxamide;
- 40 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- 45 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]isonicotinamide;
- 50 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonylbutilcarbamoyl)-2-pyridin-2-ylmethylsulfonyl)ethyl]morpholine-4-carboxamide;
- 55 2-[2*R*-(1*S*-benzoxazol-2-ylcarbonylbutilcarbamoyl)-2-morpholin-4-ylcarbonylaminoethysulfonylmethyl]pyridine-1-oxide;
- 60 1*R*-(1*S*-benzoxazol-2-ylcarbonylpentylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylcarbamate;
- 65 2*R*-[3,3-bis(2-methoxyethyl)ureido]-*N*-(1*S*-benzoxazol-2-ylcarbonylpentyl)-3-benzylsulfonylpropionamide;
- 70 *N*-[1*R*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]isonicotinamide;

N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;

N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]isonicotinamide;

5 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;

N-[1*R*-(1-benzooxazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-trifluoromethylbenzylsulfonyl)ethyl]tetrahydropyran-4-carboxamide;

10 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-3-ylmethylsulfonylethyl]pyrazine-2-carboxamide;

N-[1-(1-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]piperidine-4-carboxamide;

15 *N*-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-thien-3-ylmethylsulfonylethyl]azetidine-3-carboxamide;

N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl)butylcarbamoyl)-2-pyridin-3-ylmethylsulfonylethyl]morpholine-4-carboxamide;

20 *N*-1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethyl]piperazine-1-carboxamide;

N-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;

25 *N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylesulfonylpropylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;

N-[1*R*-(1*S*-benzooxazol-2-ylcarbonylpentylcarbamoyl)-2-benzylsulfonylethyl]piperazine-1-carboxamide;

30 *N*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropyl)-2*R*-methylsulfonylamino-3-benzylsulfonylpropionamide;

 methyl 1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-pyridin-2-ylmethylsulfonylethylcarbamate;

 methyl 1*R*-(1*S*-benzooxazol-2-ylcarbonyl-3-methylsulfonylpropylcarbamoyl)-2-benzylsulfonylethylcarbamate;

35 *N*-(1*S*-benzooxazol-2-ylcarbonylpentyl)-2*R*-[3,3-di(2-methoxyethyl)ureido]-3-pyridin-2-yl-methylsulfonylpropionamide;

- N*-[1*R*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2-(2-methoxybenzylsulfonyl)-ethyl]morpholine-4-carboxamide;
- N*-(1*S*-benzooxazol-2-ylcarbonylbutylcarbamoyl)-2*R*-(3,3-dimethylureido)-3-(2-methoxybenzylsulfonyl)propionamide;
- 5 *N*-(1*S*-benzooxazol-2-ylcarbonylbutyl)-2-methylsulfonylamino-3-(2-methoxybenzylsulfonyl)propionamide;
- benzyl 1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutylcarbamate;
- 10 *N*-[1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutyl]acetamide;
- benzyl 1*S*(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutylcarbamate;
- N*-[1*R*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethylsulfamoylmethyl)-3-methylbutyl]acetamide;
- 15 2*S*-acetylamino-*N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-cyclohexylpropionamide;
- tert*-butyl 1*S*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethyl]-2-cyclohexylethyl)carbamate;
- 20 2-acetylamino-*N*-2-benzooxazol-2-yl-1,1-dimethyl-2-oxoethyl)-3-cyclohexylpropanamide;
- benzyl 1*S*-[2-(5-phenylbenzooxazol-2-yl)-2-hydroxyethylcarbamoyl]-3-methylbutylcarbamate;
- N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenyethylethyl)-2-bicyclo[2.2.1]hept-2-ylacetamide;
- 25 *N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-2-naphthalen-1-ylacetamide;
- N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethylethyl)-3-phenylpropionamide;
- methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]-4,5-dihydrooxazole-4*S*-carboxylate;
- 30 methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]oxazole-4-carboxylate;
- N*-(2-benzooxazol-2-yl-2-hydroxy-1*S*-phenethyl)-4-cyclohexylbutyramide;

- methyl 2-[2*S*-(3-cyclohexylpropionylamino)-1-hydroxy-4-phenylbutyl]-4,5-dihydro-oxazole-4*R*-carboxylate;
- 2*S*-acetylamino-*N*-(2-benzoazol-2-yl-2-hydroxy-1*S*-phenethyl)ethyl)-3-(2-trifluoromethylphenyl)propionamide;
- 5 methyl 1-(1-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-cyclohexylethylcarbamate;
- N*-(1-benzoazol-2-ylcarbonyl-3-phenylpropyl)-3-cyclohexyl-2-methylsulfonylaminopropionamide;
- benzyl 1-(1-benzoazol-2-ylcarbonyl-3-phenylpropylsulfamoylmethyl)-2-methylbutyl
- 10 carbamate;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(6-methylpyrid-2-ylmethylsulfonyl)ethyl]thiophene-3-carboxamide;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl)-2-(2-methylpyrid-3-ylmethylsulfonyl)ethyl]nicotinamide;
- 15 *N*-[1*R*-(1*S*-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(2-cyanobenzylsulfonyl)ethyl]azetidine-3-carboxamide;
- tert*-butyl 1*R*-(1-benzoazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylcarbamate;
- tert*-butyl 1*R*-(1-benzoazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-(4-trifluoromethylpyrid-3-ylmethylsulfonyl)ethylcarbamate;
- 20 *N*-[1*R*-(1-benzoazol-2-ylcarbonylcyclobutylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethylmorpholine-4-carboxamide;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-3-ylmethylsulfonyl-ethyl]isonicotinamide;
- 25 methyl 1*R*-(1*S*-benzoazol-2-ylcarbonylbutylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethylcarbamate;
- N*-[1*R*-(1*S*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-benzylsulfonylethyl]morpholine-4-carboxamide;
- N*-(1*R*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-(3,3-dimethylureido)-3-(2-methoxybenzylsulfonyl)propionamide;
- 30 methyl 1*R*-(1*S*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-(2-methoxybenzylsulfonyl)ethylcarbamate;

- N*-(1-benzoazol-2-ylcarbonylpentyl)-2*R*-[3,3-bis(2-methoxyethyl)ureido]-3-pyridin-3-ylmethylsulfonylpropionamide;
- N*-(1*S*-benzoazol-2-ylcarbonylpentyl)-2*R*-[3,3-bis(2-methoxyethyl)ureido]-3-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)propionamide;
- 5 *N*-(1*S*-benzoazol-2-ylcarbonylpropyl)-3-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)-2*R*-methylsulfonylaminopropionamide;
- methyl 1*R*-(1*S*-benzoazol-2-ylcarbonylpropylcarbamoyl)-2-(3,5-dimethylisoxazol-4-ylmethylsulfonyl)ethylcarbamate;
- 10 *N*-[1*R*-(1-benzoazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl-ethyl]isonicotinamide;
- 4-[1*R*-(1*S*-benzoazol-2-ylcarbonylpentylcarbamoyl)-2-pyridin-2-ylmethylsulfonyl-ethylcarbamoyl]pyridine-1-oxide;
- benzyl 1*S*-[2-(4,5-dihydrooxazol-2-yl)-2-hydroxy-1*S*-phenethylcarbamoyl]-3-methylbutylcarbamate;
- 15 benzyl 1*S*-[2-(1*H*-benzoimidazol-2-yl)-2-hydroxy-1*S*-phenethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1*S*-[2-(4,5-dihydro-4*S*-phenyloxazol-2-yl)-2-hydroxy-1*S*-phenethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1*S*-(2-benzoazol-2-yl-2-hydroxy-1*S*-phenethylcarbamoyl)-3-methylbutyl
- 20 carbamate;
- benzyl 1-[2-(4,5-dihydro-5-phenyloxazol-2-yl)-2-hydroxy-1-phenethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[2-(4,5-dihydro-4*S*-methyl-5*S*-phenyloxazol-2-yl)-2-hydroxy-1-phenethylcarbamoyl]-3-methylbutylcarbamate;
- 25 benzyl 3-methyl-1-(2-hydroxy-2-naphtho[2,3-d]oxazol-2-yl-1-phenethylcarbamoyl}-butylcarbamate;
- benzyl 1*S*-(2-benzoazol-2-yl-2-hydroxy-1*S*-phenethylcarbamoyl)-2-methylpropylcarbamate;
- benzyl 1*S*-(2-benzoazol-2-yl-2-hydroxy-1*S*-phenethylcarbamoyl)-3-methylbutyl
- 30 carbamate;
- benzyl 1*S*-[2-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-2-hydroxy-1*S*-phenethylcarbamoyl]-3-methylbutylcarbamate;

- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenylbutyl]-4,5-dihydrooxazole-4-carboxylate;
- methyl 2-[2-(2,2-dimethylpropionylamino)-4-phenylbutyryl]oxazole-4-carboxylate;
- 5 *tert*-butyl 4-{1*S*-[2-(5-*tert*-butylbenzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- tert*-butyl 4-{1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-sulfamoylbenzooxazol-2-yl)ethylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- tert*-butyl 4-[1*S*-(2-hydroxy-2-naphtho[1,2-d]oxazol-2-yl)-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamoyl]piperidine-1-carboxylate;
- 10 *tert*-butyl 4-[1*S*-(2-hydroxy-2-naphtho[2,1-d]oxazol-2-yl)-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamoyl]piperidine-1-carboxylate;
- tert*-butyl 4-{1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenylbenzooxazol-2-yl)ethylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- tert*-butyl 4-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-methyl-
- 15 butylcarbamoyl]piperidine-1-carboxylate;
- tert*-butyl 3-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-methylbutylcarbamoyl]benzylcarbamate;
- tert*-butyl 4-[1*S*-(2-benzooxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-2-cyclohexylethylcarbamoyl]piperidine-1-carboxylate;
- 20 benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- pyridin-3-yl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylcarbamoyl] butylcarbamate;
- benzyl 1*S*-[2-hydroxy-1*S*-phenethyl-2-(5-phenyloxazol-2-yl)ethylsulfamoylmethyl]-2*R*-
- 25 methylbutylcarbamate;
- benzyl 3-methyl-1*S*-(1*S*-pyridin-2-ylcarbonyl-3-phenylpropylcarbamoyl)butylcarbamate;
- benzyl 1-[1-(pyridin-3-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(quinolin-3-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(1H-indol-5-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 30 benzyl 1-[1-(benzofuran-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(benzothiazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutyl-

- carbamate;
- benzyl 3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butylcarbamate;
- N*-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butyl]-4-methyl-piperazine-1-carboxamide;
- 5 *tert*-butyl 4-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butylcarbamoyl]piperazine-1-carboxylate;
- benzyl 3-methyl-1*S*-(3-phenyl-1*S*-thien-2-ylcarbonylpropylcarbamoyl)butylcarbamate;
- benzyl 1*S*-[1*S*-(1-methyl-1*H*-imidazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-methylbutylcarbamate;
- 10 benzyl 1*S*-(1*S*-thiazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylpropylcarbamate;
- N*-[3-methyl-1*S*-(3-phenyl-1*S*-thiazol-2-ylcarbonylpropylcarbamoyl)butyl]piperazine-1-carboxamide;
- benzyl 1*S*-[1*S*-(4-methylthiazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 15 benzyl 1*S*-(1*S*-furan-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1*S*-[1*S*-(1-benzyl-1*H*-imidazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 3-phenyl-1-(4,5-dihydro-4*S*-phenyloxazol-2-ylcarbonyl)propylcarbamate;
- benzyl 3-phenyl-1-(4,5-dihydro-5-phenyloxazol-2-ylcarbonylpropylcarbamate;
- 20 benzyl [1-(4,5-dihydro-4*S*-methyl-5*S*-phenyloxazol-2-ylcarbonyl)-3-phenylpropyl]-carbamate;
- ethyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]thiazole-4-carboxylate;
- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenylbutyl]oxazole-4-carboxylate;
- 25 butyl]oxazole-4-carboxylate;
- 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-1-hydroxy-4-phenylbutyl]-oxazole-4-carboxylic acid;
- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-phenylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- 30 benzyl 1-[2-(4-benzylcarbamoyloxazol-2-yl)-2-hydroxy-1-phenethylcarbamoyl]-3-methylbutylcarbamate;

- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-phenyethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 1-[1-(4,5-dihydro-4S-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 5 benzyl 1S-(1S-benzooxazol-2-ylcarbonyl-3-pentylcarbamoyl)-3-methylbutylcarbamate;
- benzyl 1S-[1S-(4,5-dihydrooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- N-[3-methyl-1S-(3-phenyl-1S-benzooxazol-2-ylcarbonylpropylcarbamoyl)butyl]-piperidine-4-carboxamide;
- 10 benzyl 1-[1-(4,5-dihydro-5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(4,5-dihydro-5S-phenyl-4S-methyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1S-(1S-phenethyl-2-benzimidazol-2-yl-1-oxoethylcarbamoyl)-3-methylbutylcarbamate;
- 15 benzyl 1-[1-(naphtho[2,3-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- methyl 2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]-4,5-dihydrooxazole-4-carboxylate;
- 20 benzyl 1S-[1S-(4,5-dihydro-4,4-dimethyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1S-(1S-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylpropylcarbamate;
- benzyl 1S-(1S-benzooxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylbutylcarbamate;
- 25 benzyl 1S-[1S-(5-chlorobenzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- N-{3-methyl-1S-[3-phenyl-1S-(5-chlorobenzooxazol-2-ylcarbonyl)propylcarbamoyl]-butyl}piperidine-4-carboxamide;
- 30 N-[2-cyclohexyl-1S-(3-phenyl-1S-benzooxazol-2-ylcarbonylpropylcarbamoyl)ethyl]-piperidine-4-carboxamide;

- methyl 2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryloxazole-4-carboxylate;
- benzyl 1-[1-(4-phenylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 5 benzyl 1-[1-(4-benzylcarbamoyloxazol-2-ylcarbonyl)-3-phenylproylcarbamoyl]-3-methylbutylcarbamate;
- tert-butyl 4{1S-[1S-(5-*tert*-butylbenzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- tert-butyl 4-{1S-[1S-(5-sulfamoylbenzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- 10 methylbutylcarbamoyl}piperidine-1-carboxylate;
- N-{3-methyl-1S-[3-phenyl-1S-(5-*tert*-butylbenzooxazol-2-ylcarbonyl)propylcarbamoyl]butyl}piperidine-4-carboxamide;
- N-{3-methyl-1S-[3-phenyl-1S-(5-sulfamoylbenzooxazol-2-ylcarbonyl)propylcarbamoyl]-butyl}piperidine-4-carboxamide;
- 15 *tert*-butyl 4-[1S-(1S-naphtho[1,2-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl)piperidine-1-carboxylate;
- tert-butyl 4-[1S-(1S-naphtho[2,1-d]oxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamoyl)piperidine-1-carboxylate;
- tert-butyl 4-{1S-[1S-(5-phenylbenzooxazol-2-ylcarbonyl)-3-phenylproylcarbamoyl]-3-methylbutylcarbamoyl}piperidine-1-carboxylate;
- 20 methylbutylcarbamoyl}piperidine-1-carboxylate;
- N-{3-methyl-1S-[3-phenyl-1S-(naphtho[1,2-d]oxazol-2-ylcarbonyl)propylcarbamoyl]butyl}piperidine-4-carboxamide;
- N-{3-methyl-1S-[3-phenyl-1S-(naphtho[2,1-d]benzooxazol-2-ylcarbonyl)propylcarbamoyl]butyl}piperidine-4-carboxamide;
- 25 N-{3-methyl-1-[3-phenyl-1-(5-phenylbenzooxazol-2-ylcarbonyl)propylcarbamoyl]-butyl}piperidine-4-carboxamide;
- benzyl 1-[1-(4-phenyethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-{1-[4-(3-phenylpropylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 30 *tert*-butyl 4-[1S-(1S-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-2-methylbutylcarbamoyl)piperidine-1-carboxylate;

- tert*-butyl 3-[1*S*-(1*S*-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-methylbutylcarbamoyl]benzylcarbamate;
- 5 *N*-[2-methyl-1*S*-(3-phenyl-1*S*-benzoxazol-2-ylcarbonylpropylcarbamoyl)butyl]-piperidine-4-carboxamide;
- 10 *N*-[2-methyl-1*S*-(3-phenyl-1*S*-benzoxazol-2-ylcarbonylpropylcarbamoyl)butyl]-3-aminomethylbenzamide;
- 15 benzyl 1-{1-[4-(2-indol-3-ylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 20 benzyl 1-[1-(4-methylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 25 benzyl 2-{2-[2-(2-benzyloxycarbonylamino-4-methylvalerylamino)-4-phenylbutyryl]-oxazol-2-ylcarbonylamino}valerate;
- 30 benzyl 1*S*-{1*S*-[4-(4-benzylpiperidin-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 35 benzyl 1*S*-[1*S*-(4-furan-2-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 40 benzyl 3-methyl-1*S*-[1*S*-(4-pyridin-2-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;
- 45 benzyl 3-methyl-1*S*-[1*S*-(4-pyridin-3-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;
- 50 benzyl 1*S*-{1*S*-[4-(2-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 55 benzyl 1*S*-{1*S*-[4-(3-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 60 benzyl 1*S*-{1*S*-[4-(4-chlorobenzylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 65 benzyl 3-methyl-1*S*-[1*S*-(4-diphenylmethyloxamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]butylcarbamate;
- 70 benzyl 1*S*-[1*S*-(4-adamantan-1-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;

- .
- benzyl 1-{1-[4-(1-methylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 1-{1-[4-(1*S*-phenylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 5 benzyl 1-{1-[4-(1*R*-phenylethylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 1-{1-[4-(*N*-benzyl-*N*-methylcarbamoyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 10 benzyl 1-[1-(4-pyrrolidin-1-ylcarbonyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-[1-(4-piperidin-1-ylcarbonyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 1-{1-[4-(2,3-dihydroindol-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- 15 benzyl 1-{1-[4-(3,4-dihydro-1*H*-isoquinolin-2-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methyl;
- benzyl 1-{1-[4-(3,4-dihydro-2*H*-quinolin-1-ylcarbonyl)oxazol-2-ylcarbonyl]-3-phenylpropylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 1-[1-(4-naphth-1-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- 20 benzyl 1-[1-(4-naphth-1-ylmethylcarbamoyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-3-methylbutylcarbamate;
- tert-butyl 4-[1*S*-(1*S*-benzooxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-2-cyclohexylethylcarbamoyl]piperidine-1-carboxylate;
- 1*S*-{1*S*-[4-(3,4-dihydro-2*H*-quinol-1-ylcarbonyl)oxazol-2-ylcarbonyl]-ethylcarbamoyl}-3-methylbutylcarbamate;
- 25 benzyl 3-methyl-1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-butylcarbamate;
- pyridin-3-yl 3-methyl-1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylcarbamoyl]-butylcarbamate;
- benzyl 1*S*-[1*S*-(5-phenyloxazol-2-ylcarbonyl)-3-phenylpropylsulfamoylmethyl]-2*R*-
- 30 methylbutylcarbamate;
- benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(3-phenylpropylcarbamoyl)oxazol-2-yl]-ethylcarbamoyl}butylcarbamate;

- benzyl 1-{2-hydroxy-2-[4-(2-indol-3-ylethylcarbamoyl)oxazol-2-yl]-1-phenethylethylcarbamoyl}-3-methylbutylcarbamate;
- benzyl 3-methyl-1-[2-hydroxy-2-(4-methylcarbamoyloxazol-2-yl)-1-phenethylethylcarbamoyl]butylcarbamate;
- 5 benzyl 2-{2-[2-(2-benzyloxycarbonylamino-4-methylvalerylanino)-1-hydroxy-4-phenylbutyl]oxazol-2-ylcarbonylamino} valerate;
- benzyl 1*S*-{2-[4-(4-benzylpiperidin-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}-3-methylbutylcarbamate;
- 10 benzyl 1*S*-[2-(4-furan-2-ylmethylcarbamoyloxazol-2-yl)-2-hydroxy-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-2-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-3-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- 15 benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-pyridin-4-ylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1*S*-{2-[4-(2-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- 20 benzyl 3-methyl-1*S*-{2-[4-(3-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1*S*-{2-[4-(4-chlorobenzylcarbamoyl)oxazol-2-yl]-2-hydroxy-1*S*-phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1*S*-{2-hydroxy-1*S*-phenethyl-2-[4-(2*R*-phenylcycloprop-1*S*-ylcarbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;
- 25 benzyl 1*S*-[2-(4-adamantan-1-ylmethylcarbamoyloxazol-2-yl)-2-hydroxy-methyl]-1*S*-phenethylethylcarbamoyl]-3-methylbutylcarbamate;
- benzyl 3-methyl-1*S*-[2-hydroxy-1*S*-phenethyl-2-(4-diphenylmethylcarbamoyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1-{2-hydroxy-2-[4-(1-methylethylcarbamoyl)oxazol-2-yl]-1-
- 30 phenethylethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(2*S*-phenyethylcarbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;

- benzyl 3-methyl-1-{2-hydroxy-1-phenethyl-2-[4-(2*R*-phenyethylcarbamoyl)oxazol-2-yl]ethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(*N*-benzyl-*N*-methylcarbamoyl)oxazol-2-yl]-2-hydroxy-1-phenethylcarbamoyl}butylcarbamate;
- 5 benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-pyrrolidin-1-ylcarbonyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- benzyl 3-methyl-1-[2-hydroxy-1-phenethyl-2-(4-piperidin-1-ylcarbonyloxazol-2-yl)ethylcarbamoyl]butylcarbamate;
- 10 benzyl 3-methyl-1-{2-[4-(2,3-dihydroindol-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(3,4-dihydro-1*H*-isoquinolin-2-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylcarbamoyl}butylcarbamate;
- benzyl 3-methyl-1-{2-[4-(3,4-dihydro-1*H*-isoquinolin-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1-phenethylcarbamoyl}butylcarbamate;
- 15 benzyl 3-methyl-1-[2-hydroxy-2-(4-naphth-1-ylmethylcarbonyloxazol-2-yl)-1-phenethylcarbamoyl]butylcarbamate;
- benzyl 1*S*-{2-[4-(3,4-dihydro-2*H*-quinol-1-ylcarbonyl)oxazol-2-yl]-2-hydroxy-1*S*-methylethylcarbamoyl}-3-methylbutylcarbamate;
- 20 *N*-[3-methyl-1*S*-(1*S*-thiazol-2-ylcarbonylethylcarbamoyl)butyl]-4-morpholin-4-ylbenzamide;
- N*-[1*S*-(2-benzooxazol-2-yl-1,1-dimethyl-2-oxoethylcarbamoyl)-3-methylbutyl]-4-(4-methylpiperazin-1-yl)benzamide;
- N*-[1*R*-(1*S*-benzooxazol-2-yl-carbonylprop-1-ylcarbamoyl)-2-(2-methylprop-1-ylsulfonyl)ethyl]morpholine-4-carboxamide;
- 25 *N*-[1*R*-(1*S*-benzooxazol-2-yl-carbonylprop-1-ylcarbamoyl)-2-cyclopropylmethylsulfonyl-ethyl]morpholine-4-carboxamide;
- N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-nicotinamide;
- N*-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-isonicotinamide;
- 30 pyridine-2-carboxylic acid-{(R)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-amide;

- pyrazine-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}$ -amide;
- $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}\text{-6-hydroxynicotinamide;}$
- 5 2-amino- $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ -nicotinamide;
- 6-amino- $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}$ -nicotinamide;
- 10 3-hydroxypyridine-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- morpholine-4-carboxylic acid- $\{(R)\text{-1-(4-cyanotetrahydropyran-4-ylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- morpholine-4-carboxylic acid- $\{(R)\text{-1-(4-cyano-1-methylpiperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 15 (R)- $N\text{-cyanomethyl-3-[2-(1,1-difluoro-methoxy)phenylmethanesulfonyl]-2-(3,3-dimethylureido)propionamide;}$
- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}$ carbamic acid allyl ester;
- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}$ carbamic acid isopropyl ester;
- 20 $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}$ carbamic acid isobutyl ester;
- $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}\text{-3,4-difluorobenzamide;}$
- 25 $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}\text{-3-methylbenzamide;}$
- thiophene-2-carboxylic acid- $\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}\}$ amide;
- 4-bromo- $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethane-sulfonyl]ethyl}\}$ benzamide;
- 30 $N\text{-}\{(R)\text{-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}\}\text{-4-methoxy-benzamide;}$

- 5 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-4-trifluoromethoxybenzamide;
- naphthalene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;
- 10 (*E*)-*N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethane-sulfonyl]ethyl}-3-phenylacrylamide;
- 5-methyl-thiophene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;
- 15 biphenyl-4-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}amide;
- 1H-indole-5-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;
- 20 benzo[1,3]dioxole-5-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;
- benzo[b]thiophene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}-amide;
- 25 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-ethyl}-3-phenoxybenzamide;
- quinoline-3-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}amide;
- 30 *N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3-(1-phenylmethanoyl)benzamide;
- 4-chloro-*N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethane-sulfonyl]-ethyl}-benzamide;
- N*-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-ethyl}-3-fluoro-4-methoxybenzamide;
- 3-bromo-thiophene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl}amide;
- 3-chlorobenzo[b]thiophene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;
- 3-chlorothiophene-2-carboxylic acid-{(*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}amide;

- N-*{(R)}*-(cyanomethylcarbamoyl)-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl}-trifluoromethyl-benzamide;
- (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-(naphthalene-2-sulfonylamino)-propionamide;
- 5 cyclopentanecarboxylic acid-*{(R)}*-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]ethyl} amide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(3-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-trifluoromethoxybenzylsulfonyl)ethyl]benzamide;
- 10 *N*-(1*R*-cyanomethylcarbamoyl-2-(3-difluoromethoxybenzylsulfonyl)ethyl]benzamide;
- N*-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide;
- N*-[1*R*-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-morpholine-4-carboxamide;
- 15 *N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;
- N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)-butyl]-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethylbenzylsulfonylmethyl)propionamide;
- N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)pentyl]-4-(2-methoxybenzenesulfonyl)-2-[2-(2-
- 20 methoxybenzenesulfonyl)ethyl]butyramide;
- 4-benzenesulfonyl-2-(2-benzenesulfonylethyl)-*N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)-butyl]butyramide;
- (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-cyclohexylmethyl-3-benzylsulfonyl-propionamide;
- 25 *N*-[(*S*)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-cyclohexyl-2-cyclohexylmethyl-propionamide;
- N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-3-isobutylsulfanyl-2-isobutylsulfanyl-
- 30 methylpropionamide;
- N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanyl-methylpropionamide;

- 5 *N*-[(*S*)-1-(1-benzoazol-2-ylmethanoyl)-butyl]-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)butyramide;
- 10 *N*-cyanomethyl-4-morpholin-4-yl-4-oxo-2-(2-trifluoromethylbenzylsulfonylmethyl)-butyramide;
- 15 *N*⁴-(4-carbamoyl-phenyl)-*N*¹-cyanomethyl-2-benzylsulfonylmethylsuccinamide;
- 20 *N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-4-morpholin-4-yl-4-oxobutyramide;
- 25 *N*-[(*S*)-1-(1-benzoazol-2-ylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 30 *N*-[(*S*)-1-(1-benzoazol-2-ylmethanoyl)pentyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 35 (*S*)-2,2-difluoro-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutanoylamino)-3-oxo-hexanoic acid dimethylamide;
- 40 *N*-[(*S*)-1-(1-benzylcarbamoylmethanoyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 45 3-biphenyl-3-yl-*N*-cyanomethyl-2-benzylsulfonylmethylpropionamide;
- 50 3-biphenyl-4-yl-*N*-cyanomethyl-2-benzylsulfonylmethylpropionamide;
- 55 3-(3-bromo-phenyl)-*N*-cyanomethyl-2-benzylsulfonylmethylpropionamide;
- 60 *N*-[(*S*)-1-((*E*)-2-benzenesulfonylvinyyl)pentyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;
- 65 *N*-[(3-benzenesulfonyl-1-phenethylallyl)-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;
- 70 *N*-cyanomethyl-3-(3-cyanobenzylsulfonyl)-2-benzylsulfonylmethylpropionamide;
- 75 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-{(*S*)-1-[1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanoyl]-propyl}-butyramide;
- 80 *N*-cyanomethyl-2-[2-1,1-difluoromethoxy)benzylsulfonylmethyl]-3-benzylsulfanyl-propionamide;
- 85 *N*-cyanomethyl-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfanyl)-propionamide;
- 90 *N*-cyanomethyl-3-isobutylsulfanyl-2-isobutylsulfanyl-methylpropionamide;
- 95 *N*-cyanomethyl-4-phenylsulfanyl-2-(2-phenylsulfanylethyl)butyramide;
- 100 *N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)benzylsulfanyl]-2-[2-(1,1-difluoromethoxy)-

- benzylsulfanyl methyl]propionamide;
- 3-benzylsulfanyl-2-benzylsulfanyl methyl-*N*-cyanomethylpropionamide;
- N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-3-benzylsulfonylpropionamide;
- 5 *N*-cyanomethyl-3-(2-trifluoromethylbenzylsulfonyl)-2-(2-trifluoromethylbenzylsulfonylmethyl)propionamide;
- 4-benzenesulfonyl-2-(2-benzenesulfonylethyl)-*N*-cyanomethylbutyramide;
- 10 *N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)benzylsulfonyl]-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]propionamide;
- 10 *N*-cyanomethyl-3-benzylsulfonyl-2-benzylsulfonylmethylpropionamide;
- 10 *N*-[(*S*)-1-(1-benzylcarbamoylmethanoyl)propyl]-3-benzylsulfonyl-2-benzylsulfonylmethylpropionamide;
- 10 *N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]-3-benzylsulfonylpropionamide;
- 15 *N*-cyanomethyl-3-(2-methylpropane-1-sulfonyl)-2-(2-methylpropane-1-sulfonylmethyl)propionamide;
- 15 acetic acid (2*S*,3*S*)-3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutanoylamino)-4-oxo-azetidin-2-yl ester;
- 15 *N*-cyanomethyl-3-(2-methylthiazol-4-ylmethylsulfonyl)-2-benzylsulfonylmethyl-
- 20 propionamide;
- 20 *N*-(3-benzenesulfonylamino-2-oxopropyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- 20 3-biphenyl-3-yl-*N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)benzylsulfonylmethyl]propionamide;
- 25 (3'-{2-(cyanomethylcarbamoyl)-3-[2-(1,1-difluoromethoxy)benzylsulfonyl]propyl}-biphenyl-4-yl)-carbamic acid ethyl ester;
- 25 *N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)-benzylsulfonylmethyl]-3-(4'-methylsulfonylaminobiphenyl-3-yl)propionamide;
- 30 3-(3-bromophenyl)-*N*-cyanomethyl-2-[2-(1,1-difluoromethoxy)phenylmethylsulfonylmethyl]propionamide;
- 30 *N*-cyanomethyl-2-((E)-3-phenyl-allyl)-3-benzylsulfonylpropionamide;
- 30 *N*-cyanomethyl-3-benzylsulfonyl-2-(3-phenylpropyl)propionamide;

- 4-morpholin-4-yl-4-oxo-N-[1-(2-oxo-2-phenylacetyl)pentyl]-2-benzylsulfonylmethylbutyramide;
- 4-morpholin-4-yl-4-oxo-N-[1-(oxophenylacetyl)pentyl]-2-benzylsulfonylmethylbutyramide as a mixture of diastereomers;
- 5 3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester;
- 4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester;
- N-(1,1-dimethyl-2-oxazolo[4,5-b]pyridin-2-yl-2-oxoethyl)-4-morpholin-4-yl-4-oxo-2-
- 10 benzylsulfonylmethylbutyramide;
- N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;
- 15 N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide;
- N-[1-(5-methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N-[1-(5-methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;
- 20 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 4-oxo-2-benzylsulfonylmethyl-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-piperidin-1-ylbutyramide;
- 25 4-oxo-2-benzylsulfonylmethyl-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-pyrrolidin-1-yl-butyramide;
- 4-oxo-2-benzylsulfonylmethyl-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]-4-piperidin-1-yl-butyramide;
- 4-morpholin-4-yl-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)propyl]-4-oxo-2-
- 30 benzylsulfonylmethylbutyramide;
- N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide;

- N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-ylbutyramide;
- 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 5 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 4-oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-ylbutyramide;
- 10 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- N-[1-(benzooxazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-ylbutyramide;
- N-[1-(benzooxazole-2-carbonyl)propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-ylbutyramide;
- 15 N-[1-(benzooxazole-2-carbonyl)propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide;
- 2-cyclohexylmethyl-4-morpholin-4-yl-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)propyl]-4-oxobutyramide;
- 20 2-cyclohexylmethyl-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)butyl]-4-morpholin-4-yl-4-oxo-butyramide;
- N-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- N-[1-(benzooxazole-2-carbonyl)propyl]-2-(2-cyclohexylethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- 25 2-(2-cyclohexylethyl)-4-morpholin-4-yl-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide;
- 2-(2-cyclohexylethyl)-4-morpholin-4-yl-4-oxo-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 30 2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propyl]butyramide;
- 2-(2-difluoromethoxybenzylsulfonylmethyl)-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide;

- N-[1-(benzoxazole-2-carbonyl)propyl]-2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide;
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]amide;
- 5 (R)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-N-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)propyl]butyramide;
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid, (S)-1-(5-phenyl-[1,2,4]oxadiazole-3-carbonyl)propyl]amide;
- 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)propyl]butyramide;
- 10 (R)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-N-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]butyramide;
- 4-morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-2-benzylsulfonylmethylbutyramide;
- 15 N-(1,1-dimethyl-2-oxazol-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide;
- N-4-isopropyl-N-1-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-2-benzylsulfonylmethylsuccinamide;
- 2-(2-difluoromethoxybenzylsulfonylmethyl)-4-morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-
- 20 3-phenylpropyl]-4-oxo-butyramide;
- 2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-butyramide;
- 25 2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-3-phenylpropyl]-4-oxo-butyramide;
- N-[1-(benzoxazole-2-carbonyl)butyl]-2-benzylsulfonyl-3-(tetrahydropyran-4-yl-oxymethyl)-propionamide;
- N-[1-(benzoxazole-2-carbonyl)butyl]-3-ethanesulfonyl-2-(tetrahydropyran-4-yl-oxymethyl)-propionamide;
- 30 N-(1-benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide;
- 2-cyclopropylmethylsulfonylmethyl-N-{(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propyl}-4-morpholin-4-yl-4-oxo-butyramide;

- N- $\{(S)\text{-}1\text{-}[(R)\text{-}(\text{hydroxy}\text{-}(3\text{-phenyl}\text{-}1,2,4\text{-oxadiazol}\text{-}5\text{-yl})\text{methyl})\text{propyl}]\text{-}2\text{-}(2\text{-methyl}\text{-}\text{propane}\text{-}1\text{-sulfonylmethyl})\text{-}4\text{-morpholin}\text{-}4\text{-yl}\text{-}4\text{-oxo}\text{-}\text{butyramide};$
- 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid
- $\{(S)\text{-}1\text{-}[(R)\text{-}(\text{hydroxy}\text{-}(3\text{-phenyl}\text{-}1,2,4\text{-oxadiazol}\text{-}5\text{-yl})\text{methyl})\text{propyl}]\text{amide};$
- 5 2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-N-[$(S)\text{-}1\text{-}(3\text{-phenyl}\text{-}1,2,4\text{-oxadiazole}\text{-}5\text{-carbonyl})\text{propyl}]\text{butyramide;}$
- 2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[$(S)\text{-}1\text{-}(3\text{-phenyl}\text{-}1,2,4\text{-oxadiazole}\text{-}5\text{-carbonyl})\text{propyl}]\text{butyramide;}$
- 10 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenylpentanoic acid,
- $(S)\text{-}1\text{-}(3\text{-phenyl}\text{-}1,2,4\text{-oxadiazole}\text{-}5\text{-carbonyl})\text{propyl}]\text{amide;}$
- 3-hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butrylamino)-azepane-1-carboxylic acid *tert*-butyl ester;
- 4-(2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butrylamino)-3-hydroxy-azepane-1-carboxylic acid *tert*-butyl ester;
- 15 3-hydroxy-4-[2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butrylamino]-azepane-1-carboxylic acid *tert*-butyl ester;
- 4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butrylamino)-3-oxo-azepane-1-carboxylic acid *tert*-butyl ester;
- 4-(2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butrylamino)-3-oxo-20 azepane-1-carboxylic acid *tert*-butyl ester;
- 4-[2-(2-methylpropane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butrylamino]-3-oxo-azepane-1-carboxylic acid *tert*-butyl ester;
- $N\text{-}(1\text{-benzenesulfonyl}\text{-}3\text{-oxo}\text{-}\text{azepan}\text{-}4\text{-yl})\text{-}4\text{-morpholin}\text{-}4\text{-yl}\text{-}4\text{-oxo}\text{-}2\text{-benzylsulfonyl}\text{-}\text{methylbutyramide;}$
- 25 $N\text{-}(1\text{-benzenesulfonyl}\text{-}3\text{-oxo}\text{-}\text{azepan}\text{-}4\text{-yl})\text{-}2\text{-}(2\text{-methylpropane}\text{-}1\text{-sulfonylmethyl})\text{-}4\text{-morpholin}\text{-}4\text{-yl}\text{-}4\text{-oxo}\text{-}\text{butyramide;}$
- $N\text{-}[(1S)\text{-}1\text{-}(benzoxazol}\text{-}2\text{-yl}\text{hydroxymethyl})\text{-}3\text{-phenylpropyl}]\text{-}2\text{-cyclopropylmethyl}\text{-}\text{sulfonylmethyl}\text{-}4\text{-morpholin}\text{-}4\text{-yl}\text{-}4\text{-oxo}\text{-}\text{butyramide;}$
- $(R)\text{-}2\text{-}((S)\text{-}1\text{-}\text{hydroxy}\text{-}2\text{-morpholin}\text{-}4\text{-yl}\text{-}2\text{-oxo}\text{-}\text{ethyl})\text{-}5\text{-phenylpentanoic acid, 1-30 (benzoxazole}\text{-}2\text{-carbonyl})\text{propyl}]\text{-}\text{amide;}$
- $(R)\text{-}5\text{-}(2\text{-difluoromethoxyphenyl})\text{-}2\text{-}((S)\text{-}1\text{-}\text{hydroxy}\text{-}2\text{-morpholin}\text{-}4\text{-yl}\text{-}2\text{-oxo}\text{-}\text{ethyl})\text{-}\text{pentanoic acid, 1-(benzoxazole}\text{-}2\text{-carbonyl})\text{-}\text{propyl}]\text{-}\text{amide;}$

- 4-morpholin-4-yl-N-[1-(oxazole-2-carbonyl)cyclopropyl]-4-oxo-2-benzylsulfonylmethyl – butyramide;
- (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-
5 propionamide;
- (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoromethoxy)phenylmethane-
sulfonyl]-2-hydroxypropionamide;
- (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-hydroxy-
propionamide;
- 10 morpholine-4-carboxylic acid (*R*)-1-(cyanomethylcarbamoyl)-2-phenylmethanesulfonyl-
ethyl ester;
- morpholine-4-carboxylic acid (*R*)-1-(cyanomethylcarbamoyl)-2-[2-(1,1-difluoro-
methoxy)phenylmethanesulfonyl]ethyl ester;
- (*R*)-(2-methoxyethyl)-carbamic acid 1-(cyanomethylcarbamoyl)-2-phenylmethanesulfonyl-
15 ethyl ester;
- (*S*)-diethylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-pyrrolidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-morpholine-4-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-4-ethyl-piperazine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl
20 ester;
- (*S*)-2-hydroxymethylpyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-
cyclohexyl-ethyl ester;
- (*S*)-(2,2,2-trifluoroethyl)carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-(2-hydroxyethyl)carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- 25 (tetrahydrofuran-2-ylmethyl)carbamic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-
ethyl ester;
- (*S*)-azetidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-cyclopropylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*S*)-piperidine-1-carboxylic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- 30 (*S*)-(2-methoxyethyl)-carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*R*)-3-hydroxypyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-
ethyl ester;

- (*S*)-3-hydroxypyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethylcarbamoyl)-2-cyclohexyl-ethyl ester;
- (*S*)-morpholine-4-carboxylic acid 1-(cyanomethylcarbamoyl)-3-cyclohexylpropyl ester;
- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-
- 5 propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propyl-
carbamoyl]-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl ester;
- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzothiazol-2-ylmethanoyl)propyl-
carbamoyl]-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]ethyl ester;
- 10 pyrrolidine-1-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propyl-
carbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
- dimethyl-carbamic acid (*R*)-1-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propylcarbamoyl]-2-
phenylmethanesulfonylethyl ester;
- morpholine-4-carboxylic acid (*R*)-1-[*(S)*-1-(1-benzylcarbamoylmethanoyl)propyl-
- 15 carbamoyl]-2-phenylmethanesulfonylethyl ester;
- morpholine-4-carboxylic acid (*S*)-1-[*(S)*-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-
propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- morpholine-4-carboxylic acid (*S*)-1-[*(S)*-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-
propylcarbamoyl]-2-phenylmethanesulfonylethyl ester;
- 20 (*S*)-2-{(*R*)-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-2-hydroxy-propanoyl-
amino}-*N*-methoxy-*N*-methylbutyramide;
- (*R*)-3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]-*N*-((*S*)-1-formylpropyl)-2-
hydroxy-propionamide;
- (*R*)-*N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)propyl]-2-hydroxy-3-phenylmethane-
- 25 sulfonylpropionamide;
- (*S*)-3-{3-[2-(1,1-difluoromethoxy)phenylmethanesulfonyl]propanoylamino}-2-oxo-
pentanoic acid benzylamide;
- N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-propyl]-3-[2-(1,1-difluoromethoxy)phenyl-
methanesulfonyl]-propionamide;
- 30 *N*-[*(S)*-1-(1-benzooxazol-2-ylmethanoyl)-3-phenylpropyl]-3-*p*-tolylmethanesulfonyl-
propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-

- propyl)propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-5 propyl)propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-1*H*-thiomorpholin-4-yl)-1-ethyl-2,3-dioxopropyl]propionamide;
- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methylsulfonylpiperazin-1-yl)-2,3-dioxopropyl]propionamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid dimethylamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid 15 phenylamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)amide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)propionylamino]-2-oxo-pentanoic acid (1-20 benzoyl-piperidin-4-yl)amide;
- 3-[3-(2-difluoromethoxyphenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-ylethyl)amide;
- (*R*)-*N*-[(*S*)-1-(1-benzoazol-2-ylmethanoyl)propyl]-2-(2-nitrophenylamino)-3-25 phenylmethanesulfonylpropionamide;
- N*-[1-(benzoazole-2-carbonyl)propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-yl-amino)-propionamide.
- (*R*)-*N*-[(*S*)-1-(1-benzoazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide;
- (2S)-(4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(*S*)-cyano-3-phenyl-propyl)-30 amide;

- N*-(1(*S*)-cyano-3-phenyl-propyl)-2-(*S*)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenylbutyramide;
- N*-(1(*S*)-cyano-3-phenylpropyl)-2-(*S*)-fluoro-4-phenylbutyramide;
- N*-(1(*S*)-cyano-3-phenylpropyl)-2,2-difluoro-4-phenylbutyramide;
- 5 *N*-(1(*S*)-cyano-3-phenylpropyl)-2-(*S*)-hydroxy-4-phenylbutyramide;
- N*-(1(*S*)-cyano-3-phenylpropyl)-2-(*R*)-hydroxy-4-phenylbutyramide;
- N*-(1(*S*)-cyano-3-phenylpropyl)-2-(*R*)-methoxy-4-phenylbutyramide;
- 2,2-difluoro-5-phenylpentanoic acid (1-cyanocyclopropyl)-amide;
- N*-(1(*S*)-cyano-3-phenylpropyl)-4-phenylbutyramide;
- 10 2,2-difluoro-5-phenylpentanoic acid ((*S*)-1-cyano-3-phenylpropyl)amide;
- N*-(4-cyano-1-ethylpiperidin-4-yl)-3-cyclohexylpropionamide;
- N*-(4-cyano-1-ethylpiperidin-4-yl)-3-(2-difluoromethoxyphenylmethanesulfonyl)-
- propionamide;
- (*S*)-*tert*-butylcarbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- 15 (*R*)-carbamic acid 1-(cyanomethylcarbamoyl)-2-(2-difluoromethoxy-
- phenylmethanesulfonyl)ethyl ester;
- (*S*)-carbamic acid 1-(cyanomethylcarbamoyl)-2-cyclohexylethyl ester;
- (*R*)-morpholine-4-carboxylic acid 1-(1-cyanocyclopropylcarbamoyl)-2-
- phenylmethanesulfonylethyl ester;
- 20 (*R*)-morpholine-4-carboxylic acid 1-(4-cyanotetrahydropyran-4-ylcarbamoyl)-2-
- phenylmethanesulfonylethyl ester;
- 3-cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propyl]propionamide;
- (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-2-isopropylamino-3-phenylmethanesulfonyl-
- propionamide;
- 25 (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-
- propionamide;
- (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-2-dimethylamino-3-phenylmethanesulfonyl-
- 30 propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-
- pyran-4-ylamino)propionamide;

- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(1-methylpiperidin-4-ylamino)-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(bis-thiophen-2-ylmethylamino)-3-phenylmethanesulfonylpropionamide;
- 5 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-dibenzylamino-3-phenylmethanesulfonylpropionamide;
- (*S*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-(tetrahydropyran-4-ylamino)-3-thiophen-2-ylpropionamide;
- 10 (*S*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-isopropylamino-3-thiophen-2-ylpropionamide;
- (*R*)-*N*-[1-(benzothiazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)propionamide;
- 15 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-isopropylamino-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-[(2-methoxyethyl)-(tetrahydropyran-4-yl)-amino]-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethane-
- 20 sulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)butyl]-2-dimethylamino-3-phenylmethanesulfonylpropionamide;
- (1*S*)-*N*-[1-(benzoxazole-2-carbonyl)butyl]-2-(*S*)-fluoro-4-phenylbutyramide;
- 2,2-difluoro-5-phenylpentanoic acid [*(S*)-1-(benzoxazole-2-carbonyl)butyl]amide;
- 25 morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(benzoxazole-2-carbonyl)propylcarbamoyl]-2-cyclohexyl-ethyl ester;
- morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)propylcarbamoyl]ethyl ester;
- morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-
- 30 carbonyl)propylcarbamoyl]ethyl ester;
- morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)propylcarbamoyl]ethyl ester;

- morpholine-4-carboxylic acid (*S*)-1-[*(S*)-1-(benzoxazole-2-carbonyl)propylcarbamoyl]-3-cyclohexylpropyl ester;
- 4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester;
- 5 (*R*)-*N*-[*(S*)-1-(benzoxazole-2-carbonyl)butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethane-sulfonylpropionamide;
- (*R*)-*N*-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethane-sulfonylpropionamide;
- 10 (*R*)-3-phenylmethanesulfonyl-*N*-[*(S*)-3-phenyl-1-(thiazole-2-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[*(S*)-1-(benzoxazole-2-carbonyl)-3-phenylpropyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 15 (*R*)-3-cyclopropylmethanesulfonyl-*N*-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-3-phenylmethanesulfonyl-*N*-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)propyl]-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-
- 20 2-(tetrahydropyran-4-ylamino)propionamide;
- {(*R*)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethane-sulfonylethyl} carbamic acid *tert*-butyl ester;
- 25 {(*S*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-thiophen-2-ylethyl}-carbamic acid *tert*-butyl ester;
- {(*R*)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethane-
- 30 sulfonylethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-ylhydroxymethyl)butylcarbamoyl]-2-cyclopropylmethane-sulfonylethyl} carbamic acid *tert*-butyl ester;

- (*R*)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propylcarbamoyl}-2-phenylmethanesulfonylethyl)-carbamic acid *tert*-butyl ester;
- ((*R*)-2-cyclopropylmethanesulfonyl-1-{(*S*)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)hydroxymethyl]propylcarbamoyl}ethyl)carbamic acid *tert*-butyl ester;
- 5 {(*R*)-1-[1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethanesulfonylethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)-3-phenylpropylcarbamoyl]-2-cyclopropylmethanesulfonylethyl}-carbamic acid *tert*-butyl ester;
- 10 {(*R*)-1-[*(S*)-1-(hydroxythiazol-2-ylmethyl)-3-phenylpropylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-cyclopropylmethanesulfonylethyl}-carbamic acid *tert*-butyl ester;
- (*R*)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]propylcarbamoyl}-2-phenylmethanesulfonylethyl)-carbamic acid *tert*-butyl ester;
- 15 ((*R*)-2-cyclopropylmethanesulfonyl-1-{(*S*)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)hydroxymethyl]propylcarbamoyl}ethyl)carbamic acid *tert*-butyl ester;
- {(*R*)-1-[1-(benzoxazol-2-yl-hydroxymethyl)butylcarbamoyl]-2-phenylmethanesulfonylethyl} carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(benzoxazol-2-yl-hydroxymethyl)-3-phenylpropylcarbamoyl]-2-
- 20 cyclopropylmethanesulfonylethyl}-carbamic acid *tert*-butyl ester;
- {(*R*)-1-[*(S*)-1-(hydroxythiazol-2-yl-methyl)-3-phenylpropylcarbamoyl]-2-phenylmethanesulfonylethyl} carbamic acid *tert*-butyl ester;
- (*R*)-2-phenylmethanesulfonyl-1-{(*S*)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)hydroxymethyl]propylcarbamoyl}ethyl)carbamic acid *tert*-butyl ester;
- 25 (*R*)-*N*-[1-(benzoxazole-2-carbonyl)butyl]-2-[cyclopropylmethyl](tetrahydropyran-4-ylmethyl)amino]-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[1-(benzothiazol-2-yl-hydroxymethyl)butyl]-2-dibenzylamino-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-30 pyran-4-ylamino)propionamide;
- (*R*)-*N*-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide;

- (*R*)-*N*-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-2-dimethylamino-3-phenylmethane-sulfonyl-propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 5 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-yl-hydroxymethyl)butyl]-2-(1-methylpiperidin-4-ylamino)-3-phenylmethanesulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-(bis-thiophen-2-ylmethylamino)-3-phenylmethanesulfonylpropionamide;
- 10 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-dibenzylamino-3-phenylmethane-sulfonylpropionamide;
- (*S*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-(tetrahydropyran-4-ylamino)-3-thiophen-2-yl-propionamide;
- (*S*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide;
- 15 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-yl-hydroxymethyl)butyl]-2-isopropylamino-3-phenylmethane-sulfonylpropionamide;
- (*R*)-*N*-[1-(benzothiazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- 20 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-3-phenylmethanesulfonyl-2-(tetrahydropyran-4-ylamino)propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-[(2-methoxyethyl)-(tetrahydro-pyran-4-yl)amino]-3-phenylmethanesulfonylpropionamide;
- 25 (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-cyclohexylamino-3-phenyl-methanesulfonyl-propionamide;
- (*R*)-*N*-[(*S*)-1-(benzoxazol-2-ylhydroxymethyl)butyl]-2-dimethylamino-3-phenylmethane-sulfonyl-propionamide;
- N*-cyanomethyl-3-cyclohexylpropionamide;
- 30 *N*-cyanomethyl-3-(2-difluoromethoxyphenylmethanesulfonyl)propionamide;
- 3-(3-cyclohexylpropionylamino)-2-oxo-5-phenylpentanoic acid thiazol-2-ylamide;
- 3-cyclohexyl-*N*-(1-formyl-3-phenylpropyl)propionamide;

- 3-(2-difluoromethoxyphenylmethanesulfonyl)-*N*-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)propyl]propionamide;
- N*-[(*S*)-1-(benzooxazole-2-carbonyl)propyl]-2-(2-cyanophenylamino)-3-cyclohexyl-propionamide;
- 5 *N*-Cyanomethyl-3-cyclohexyl-2-(4-methoxyphenoxy)propionamide;
- 2-benzylxy-*N*-cyanomethyl-3-cyclohexylpropionamide;
- (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-benzylxy-3-phenylmethane-sulfonylpropionamide;
- (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenyl-10 methanesulfonylpropionamide;
- (*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)butyl]-2-hydroxy-3-phenylpropionamide;
- (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-ylmethanoyl)propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxypropionamide;
- (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-2-hydroxy-3-phenylmethanesulfonyl-15 propionamide;
- (*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(*S*)-1-(1-pyridazin-3-ylmethanoyl)butyl]-propionamide;
- (*S*)-3-((*R*)-2-hydroxy-3-phenylmethanesulfonylpropanoylamino)-2-oxo-pentanoic acid benzylamide;
- 20 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)propyl]-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-hydroxypropionamide;
- (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-ylmethanoyl)propyl]-3-[2-(1,1-difluoromethoxy)-phenylmethanesulfonyl]-2-hydroxypropionamide;
- (2*R*,5*S*)-2-[2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-25 morpholin-3-one;
- (*S*)-*N*-[(*S*)-1-(benzoxazol-2-ylcarbonyl)-propyl]-3-cyclohexyl-2-(1,1-dioxo-benzo[d]isothiazol-3-ylamino)propionamide;
- 2-(1,1-dioxobenzo[d]isothiazol-3-ylamino)-4-methyl-pentanoic acid [1-(benzoxazol-2-ylcarbonyl)propyl]amide;
- 30 (*S*)-4-methyl-2-(3-oxo-3*H*-isoindol-1-ylamino)-pentanoic acid (*S*)-[1-(benzoxazol-2-ylcarbonyl)propyl]amide;

- ({1(S)-(1(S)-benzoxazol-2-ylcarbonyl)propylcarbamoyl]-3-methylbutylamino}-morpholin-4-ylmethlene)carbamic acid ethyl ester;
- N-[1-(benzoxazol-2-yl-hydroxy-methyl)-propyl]-3-cyclohexyl-2-{[N-(2,2,2-trifluoroethyl)-morpholine-4-carboximidoyl]-amino}-propionamide;
- 5 N-[1(S)-(benzoxazol-2-ylcarbonyl)-propyl]-3-phenylmethanesulfonyl-2(R)-{[N-(2,2,2-trifluoroethyl)-morpholin-4-ylcarboximidoyl]amino} propionamide;
- N-[1-(benzoxazol-2-ylcarbonyl)propyl]-3-cyclohexyl-2(S)-[N-(2,2,2-trifluoroethyl)-formimidoylamino]propionamide;
- 10 N-[1-(benzoxazol-2-ylcarbonyl)propyl]-3-cyclohexyl-2(S)-[(methanesulfonyliminophenyl-methyl)amino]propionamide;
- N-[1-(benzoxazol-2-ylcarbonyl)propyl]-2(R)-(1-cyclopentylamino-2-methanesulfonyl-vinylamino)-3-cyclopropylmetanesulfonylpropionamide;
- N-[1-(benzoxazol-2-ylcarbonyl)-propyl]-3-cyclohexyl-2(S)-[(morpholin-4-yl-carboximidoyl)amino]propionamide;
- 15 N-[1(S)-(benzoxazol-2-ylhydroxymethyl)propyl]-3-cyclohexyl-2(S)-[(methanesulfonyl-iminomethyl)amino]propionamide;
- {1-[1(S)-(benzoxazol-2-ylcarbonyl)-propylcarbamoyl]-2(R)-phenylmethane-sulfonylethylamino} phenylmethylenecarbamic acid ethyl ester; or
- a pharmaceutically acceptable salts thereof.

20

ABSTRACT

The present invention is directed to the use of Cathepsin S inhibitors in combination with a biologic that elicits an immune response in patients receiving the biologic.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/041580

International filing date: 10 December 2004 (10.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/528,846
Filing date: 11 December 2003 (11.12.2003)

Date of receipt at the International Bureau: 24 January 2005 (24.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record.**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
 - IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
 - FADED TEXT OR DRAWING**
 - BLURRED OR ILLEGIBLE TEXT OR DRAWING**
 - SKEWED/SLANTED IMAGES**
 - COLOR OR BLACK AND WHITE PHOTOGRAPHS**
 - GRAY SCALE DOCUMENTS**
 - LINES OR MARKS ON ORIGINAL DOCUMENT**
 - REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
 - OTHER:** _____
-

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.